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ABOUT COVER

Peer Review of *World Journal of Stem Cells*, Asmaa Mohammed Shamseldeen, MD, Assistant Professor, Department of Physiology, Cairo University, Cairo 30411, Egypt. asmaa82shamseldeen@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc*.

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REVIEW

Wharton's jelly mesenchymal stem cells: Future regenerative medicine for clinical applications in mitigation of radiation injury

Prashasti Sharma, Dharmendra Kumar Maurya

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Abstract

Wharton's jelly mesenchymal stem cells (WJ-MSCs) are gaining significant attention in regenerative medicine for their potential to treat degenerative diseases and mitigate radiation injuries. WJ-MSCs are more naïve and have a better safety profile, making them suitable for both autologous and allogeneic transplantations. This review highlights the regenerative potential of WJ-MSCs and their clinical applications in mitigating various types of radiation injuries. In this review, we will also describe why WJ-MSCs will become one of the most probable stem cells for future regenerative medicine along with a balanced view on their strengths and weaknesses. Finally, the most updated literature related to both preclinical and clinical usage of WJ-MSCs for their potential application in the regeneration of tissues and organs will also be compiled.

Key Words: Stem cells; Wharton's jelly mesenchymal stem cells; Radiotherapy; Xerostomia; Lung fibrosis

Core Tip: Stem cells, particularly Wharton's jelly mesenchymal stem cells (WJ-MSCs), are pivotal in cell-based therapy due to their robust tissue repair abilities. While radiotherapy is a common cancer treatment, it often causes collateral damage to healthy tissues, reducing its efficacy. WJ-MSCs, resembling embryonic stem cells, exhibit superior differentiation and safety, making them ideal for both autologous and allogeneic transplants. This review emphasizes WJ-MSCs' regenerative potential and clinical utility in alleviating radiation-induced injuries resulting from radiotherapy across various cancer types.

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INTRODUCTION

Cancer cells are very aggressive in nature and hold their place in the top five most common causes of death worldwide [1]. Some of the common strategies being used in cancer treatment include radiotherapy (RT), chemotherapy, surgery, and their combinations. However, nowadays, RT is one of the main treatment modalities for treating cancer patients, either alone or in combination with chemotherapy and surgery[2]. RT is used as a definitive treatment or employed either to reduce tumor size before surgery or after surgery to eradicate small masses of tumor cells that remain after surgery, depending on the type of cancer[3,4]. There are diverse types of radiation therapies, such as external beam RT, brachytherapy, systemic radioisotope therapy, stereotactic body RT, stereotactic radiosurgery, proton, heavy particles RT, as well as fractionation regimens (*e.g.*, hypofractionation, hyperfractionation, and accelerated fractionation)[5]. RT is one of the preferred treatment options for patients with solid tumors. While RT invariably exposes healthy cells to radiation along with the cancer cells and leads to different types of radiation injuries, several advancements, such as intensity-modulated RT (IMRT) or image-guided RT, have significantly reduced the normal tissue damage associated with conventional RT. However, healthy tissues lying in the path of radiation still get exposed. Therefore, there is still a need for a treatment modality that can regenerate the tissue damage caused by radiation exposure during treatment.

Currently, researchers have identified several strategies to address normal tissue damage caused by RT, including the development of radiation protectors and mitigators. Radioprotective agents, such as amifostine, protect normal tissues by scavenging free radicals and enhancing DNA repair, although further exploration is needed to fully understand their mechanisms and minimize side effects[6]. Fractionation, which involves dividing the total radiation dose into smaller sessions, allows normal cells time to repair, yet optimal schedules and individualized responses are areas for deeper study[7]. Advanced radiation techniques like IMRT and image-guided RT provide precise targeting to spare healthy tissues, though their long-term impacts and best practices require further investigation. Proton therapy, which precisely deposits radiation at the tumor site, minimizes collateral damage, but its cost-effectiveness and comparative efficacy need more comprehensive evaluation[8]. Present interventions for radiation-induced normal tissue damage include physical modalities, such as modified collimators and fractionation schedules, and pharmacological agents like essential fatty acids, vasoactive drugs, and antioxidants[9]. However, these procedures need more standardization. Notably, stem cell therapy, especially with mesenchymal stem cells (MSCs) has emerged as a highly promising approach for promoting tissue repair and regeneration post-radiation exposure[10]. Radiation-driven injuries cause significant damage at the cellular and molecular levels, leading to severe inflammation, tissue destruction, and impaired healing processes[11]. The body's response to such injuries involves the release of cytokines and chemokines, which play crucial roles in signaling and attracting stem cells to the damaged sites[12]. These molecular mechanisms create an environment conducive to stem cell therapies, as the recruited stem cells can differentiate into various cell types, promote tissue regeneration, and favorably modulate inflammatory responses. This makes stem cell therapy particularly suitable for treating radiation-induced damage, offering potential for effective repair and recovery of affected tissues[10]. The potential of MSCs to enhance healing while minimizing adverse effects marks a significant advancement in RT support, though further research is needed to optimize cell types, dosages, and delivery methods[10].

In the last two decades, the use of stem cells in the field of regenerative medicine has significantly increased because of their tremendous regenerative potential. Stem cells became integral to modern regenerative medicine in the 1950s, notably with the first successful bone marrow transplantation in 1956. This breakthrough hinted at future treatment possibilities, encouraging the refinement of clinical techniques[13]. While today stem cells are at the forefront of regenerative medicine with their unlimited division potential and ability to trans-differentiate, they hold promise as a leading source for repairing tissues and organs[14]. Several clinical trials are currently underway in the field of stem cell therapeutics[15]. Until now, stem cells have been isolated from various sources ranging from blastocysts to adult tissues. We can now induce the dedifferentiation of adult cells into pluripotent stem cells by expressing the pluripotency transcription factors Sox2, Oct3/4, cMyc, and Klf4[16]. Stem cells are categorized into embryonic stem cells (ESCs) and adult stem cells (ASCs) including fetal stem cells according to their respective origins[17]. Induced pluripotent stem cells (iPSCs) represent a class of pluripotent stem cells that can be generated from adult somatic cells through a process of "reprogramming", accomplished by the transduction of pluripotency genes[16]. The isolation of ESCs poses many ethical issues compared to ASCs. At the same time, ESCs/iPSCs have limitations due to associated risks of immune rejection, teratoma formation, and tumorigenesis[18]. Different sources of stem cells have inherent advantages and disadvantages in terms of their derivation, potency, and biological efficacy[16-21] (Table 1). ASCs also referred to as somatic or tissue stem cells, are uncommon cell populations residing in the body throughout a significant portion of postnatal life. These cells play a crucial role in generating a limited range of mature cell types specific to the tissue they inhabit. These are again majorly classified into hematopoietic stem cells (HSCs) and MSCs on the basis of origin (Figure 1). HSCs isolated from the bone marrow have limited plasticity and can only differentiate into blood and blood-related lineages. On the other hand, MSCs are adaptable stromal cells with multipotent characteristics, possessing the ability to differentiate into various cell types such as adipocytes, myocytes, osteocytes, and chondrocytes[22]. The isolation of bone marrow MSCs (BM-MSCs) in the 1960s-1970s opened up new possibilities for their application[18] and has become one of the most

Table 1 Different types of stem cells and their characteristics

Characteristics	Embryonic stem cells	Induced pluripotent stem cells	Adult stem cells	Ref.
Origin	Inner cell mass of blastocyst	Somatic cells	Postnatal adult tissue	[16]
Potency	Pluripotent	Pluripotent	Multipotent	[17]
Self-renewal	Yes	Yes	Limited	[17]
Teratoma formation	Yes	Yes	No	[18]
Tumorigenesis	Yes	Yes	No	[18]
Immune response	Immuno-privileged MHC-I and II present in low level	Not immuno-privileged MHC-I and II present in normal level	MSCs are immuno-privileged and immunosuppressive in nature	[18,19,20,21,22]
Ethical issue	Serious ethical issue	No ethical issue	No ethical issue	[21]

MHC: Major histocompatibility class; MSC: Mesenchymal stem cell.

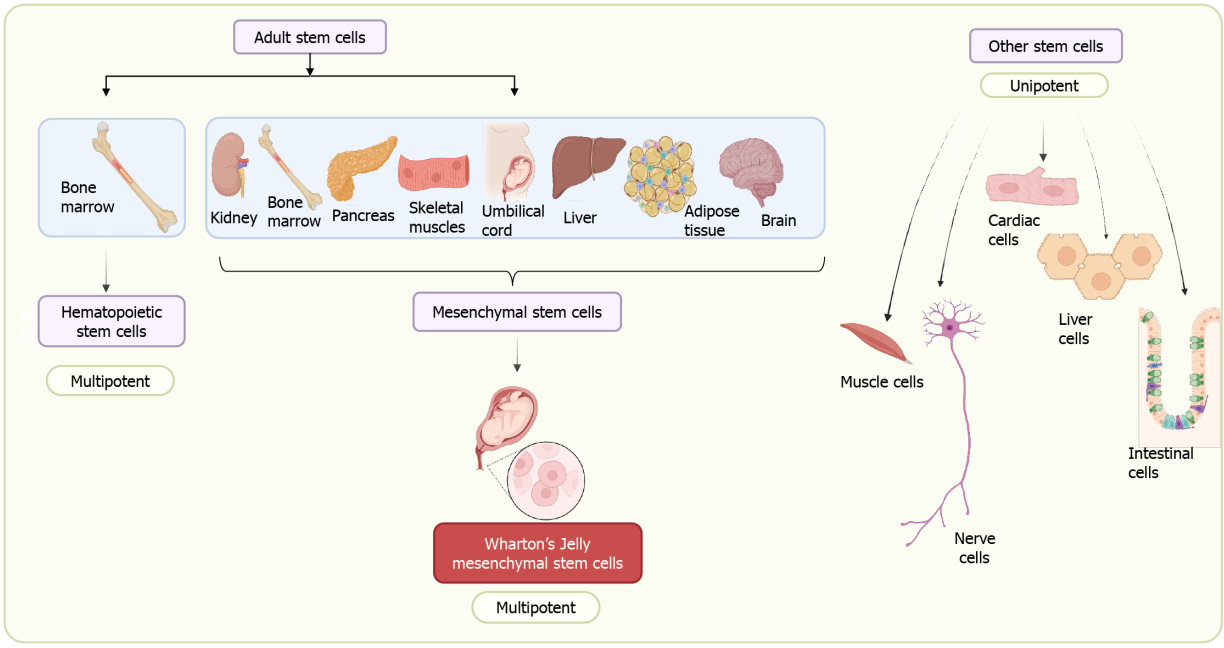

Figure 1 Illustration of diverse stem cell types with varying differentiation capacities. Adult stem cells, typically multipotent, differ based on their organ source, *e.g.*, Hematopoietic stem cells in bone marrow and mesenchymal stem cells in various tissues, including Wharton's jelly from the umbilical cord. In contrast, unipotent cells specialize in specific tissues like muscles, nerves, and more (created with BioRender.com).

studied MSCs since[19,23]. Subsequently, alternative sources of MSCs were explored, such as adipose tissue, dental pulps, and extra-embryonic tissues like the placenta, umbilical cord, and amnion. Table 2 shows a comparison of the three most commonly used MSCs. MSCs isolated from extra-embryonic tissues are more naïve and share features with ESCs compared to other MSCs. They have immuno-privileged characteristics, possess broader multipotent plasticity, and proliferate faster compared to adult MSCs[20,24]. The isolation of stem cells from the umbilical cord opens up several opportunities in the field of regenerative medicine. In this review, we mainly focus on MSCs isolated from Wharton's jelly (WJ) of umbilical cord, which have tremendous therapeutic potential due to their inherent repair and regenerative abilities. Our emphasis will be on the possible applications of umbilical cord MSCs (UC-MSCs) in mitigating radiation injuries. We will first discuss their origin and unique features and then explore their possible applications in the treatment of different types of radiation injuries and their underlying mechanisms. Finally, we will discuss the challenges and future perspectives of MSCs found in the umbilical cord.

WJ-MSC IN REGENERATIVE MEDICINE

Origin of WJ-MSCs

For decades, WJ-MSCs have seemed to be of particular interest because they can be harvested after delivery without any

Table 2 Characteristic feature of major mesenchymal stem cells

Characteristics	BM-MSCs	AD-MSCs	UC-MSCs	Ref.
Harvesting procedure	Invasive	Invasive	Non-invasive	[18]
Potency to differentiate	Low	Low	High	[18,20]
Proliferative potential	Low	Low	High	[18,20,21]
Immune modulatory properties	Good	Good	Good	[18]
Allogenic cell rejection	No	No	No	[18,22]
Ethical issue	No	No	No	[23]
Risk of tumorigenicity	No	No	No	[18]

BM-MSC: Bone marrow mesenchymal stem cell; AD-MSC: Adipose-derived mesenchymal stem cell; UC-MSC: Umbilical cord mesenchymal stem cell.

ethical issues. They have the capacity to expand at a faster rate than adult MSCs, in which expansion declines with aging, and they start showing immunological issues. Anatomically, the umbilical cord contains a specific mucous proteoglycan-rich matrix known as WJ. Within this matrix, there are two umbilical arteries and one umbilical vein, and the whole structure is covered by amniotic epithelium (Figure 2). The umbilical cord connects the developing baby with the placenta in the womb and supplies oxygen and nutrient-rich blood to sustain its growth. WJ, confined in the umbilical cord, prevents umbilical vessels from twisting, compression, or torsion during fetal movement, safeguarding proper blood supply to the fetus[25]. This unique anatomic architecture of the umbilical cord allows communication between the mother and the fetus through the fetoplacental membrane, hormone and cytokine interaction[26]. During fetal development, hematopoiesis takes place in the yolk sac and later in the aorta-gonad-mesonephros region, and these processes are linked to the presence of stem cells in the cord. There are two possible theories on the presence of stem cells in the umbilical cord: (1) Migration of fetal HSCs and MSCs toward the placenta, and during a second round of migration from the placenta to the liver and bone marrow, some cells get trapped and reside in the WJ of the umbilical cord[27]; or (2) These MSCs originate from mesenchyme already present in the umbilical cord matrix. Thus, these MSCs trapped in the WJ remain there for the duration of the gestational period[27]. Different researchers have named these MSCs with different names such as UC-MSCs, umbilical cord stem cells, WJ stem cells, or WJ-MSCs. Among all these names, WJ-MSCs is the most common. WJ-MSCs can be isolated from three regions: The perivascular zone, the intervascular zone, and the sub-amnion[28]. Studies show significant differences in the number and nature of stem cells among these three regions[29,30].

Unique features of the WJ-MSCs

WJ-MSCs are a kind of multipotent stem cells that have several common features of ESCs. Their potency lies between pluripotent and multipotent stem cells (Figure 3). They significantly express ESC stemness markers Oct-4, Sox-2, and Nanog[31]. WJ-MSCs comply with all the measures of the International Society for Cellular Therapy for MSCs[32,33]. These criteria are as follows: Adherence to treated plastic for cell culture (polystyrene), morphologically spindle-shaped [34], high expression of MSCs markers such as CD29, CD44, CD73, CD90, CD105, and no expression of hematopoietic and endothelial markers such as HLA-DR, CD11b, CD14, CD31, CD34, and CD45, and *in vitro* tri-lineage differentiation potential (such as osteocytes, chondrocytes, and adipocytes)[35,36].

The amount of MSCs that can be obtained from bone marrow is very limited. Only 0.001% to 0.01% of mononuclear cells have been reported[23], while 1 g of adipose tissue yields approximately 5×10^3 stem cells, which is 500-fold greater than in the bone marrow[37]. The isolation efficiency from WJ is high and ranges from (1-5) $\times 10^4$ cells/cm of umbilical cord[38]. WJ-MSCs have several advantages, such as cost-effectiveness, unlimited availability of tissue sources, easy collection, convenient transportation, no donor site morbidity, and highly proliferative potential without losing potency and functions, which make them superior to other sources of MSCs[39].

Immuno-privileged eminence of WJ-MSCs

WJ-MSCs are multipotent, immunosuppressive, non-tumorigenic, and highly suitable for allogeneic and xenogeneic transplantation compared to other sources of MSCs[18,28,31,40]. WJ-MSCs are also capable of immune suppression and immune avoidance, similar to other types of MSCs. They are non-immunogenic because they express low levels of major histocompatibility class (MHC) I (HLA-ABC) and do not express MHC-II (HLA-DR) and co-stimulatory antigens (CD80, CD86) associated with the stimulation of both T and B cell reactions[40-43]. The low levels of expression of MHC class I protect WJ-MSCs from natural killer cell-mediated lysis[41]. Although BM-MSCs and WJ-MSCs are both MSCs, HLA-DR is considerably induced in BM-MSCs with interferon (IFN)-γ treatment, whereas this induction is very negligible in WJ-MSCs[42,44-46]. In addition, WJ-MSCs produce large amounts of tolerogenic factors such as interleukin (IL)-10, higher levels of transforming growth factor (TGF)-β, and express HLA-G, which is not true for BM-MSCs[40,42-44]. They also express high levels of leukocyte antigen G6 (HLA-G6), which is produced by trophoblasts and protects the embryo from immune-based destruction[43]. WJ-MSCs release secretory soluble mediators such as IL-6, IL-8, TGF-β, indoleamine-2,3-dioxygenase (IDO), vascular endothelial growth factor (VEGF), cyclooxygenase-2, prostaglandin E2 (PGE2), hepatocyte

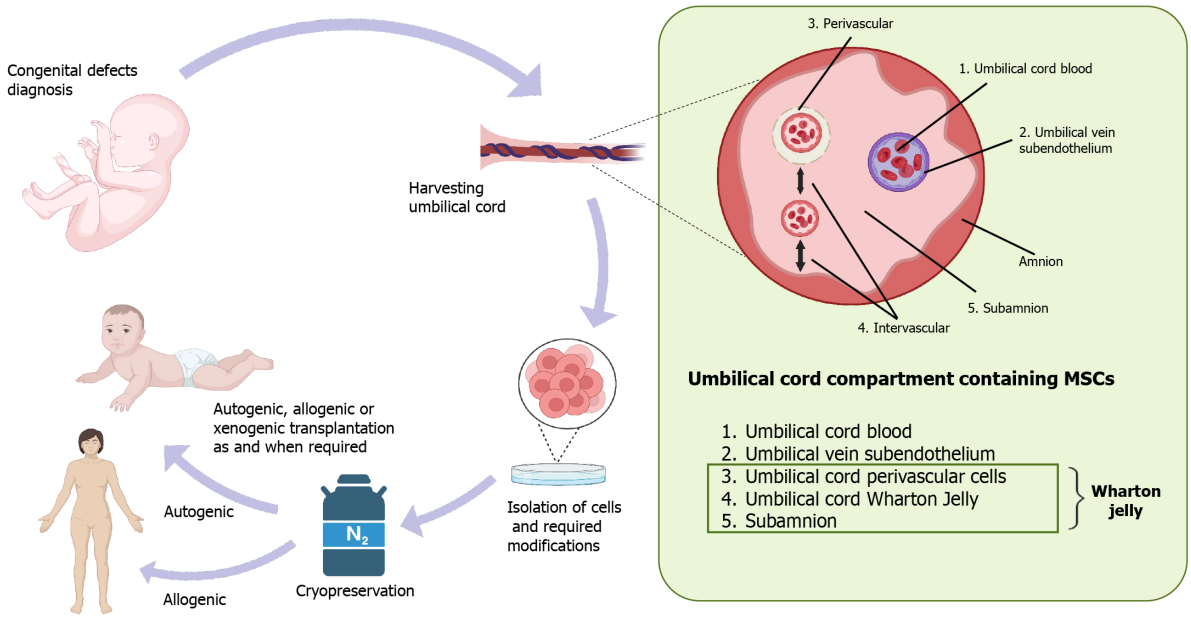

Figure 2 Wharton's jelly mesenchymal stem cells. Wharton's jelly contains a large number of multipotent stem cells. The cord's cross-sectional view reveals five distinct regions rich in mesenchymal stromal cells: (1) Umbilical cord blood; (2) Wharton's jelly mesenchymal stem cells (MSCs) from umbilical vein subendothelium; (3) Perivascular zone; (4) Intravascular space; and (5) The subamnion region thrives. Zones 3 to 5 belong to Wharton's jelly. These potent cells, once extracted, can be tailored for various uses, cryopreserved for future needs, or utilized in autogenic, allogenic, or xenogeneic transplants (created with BioRender.com).

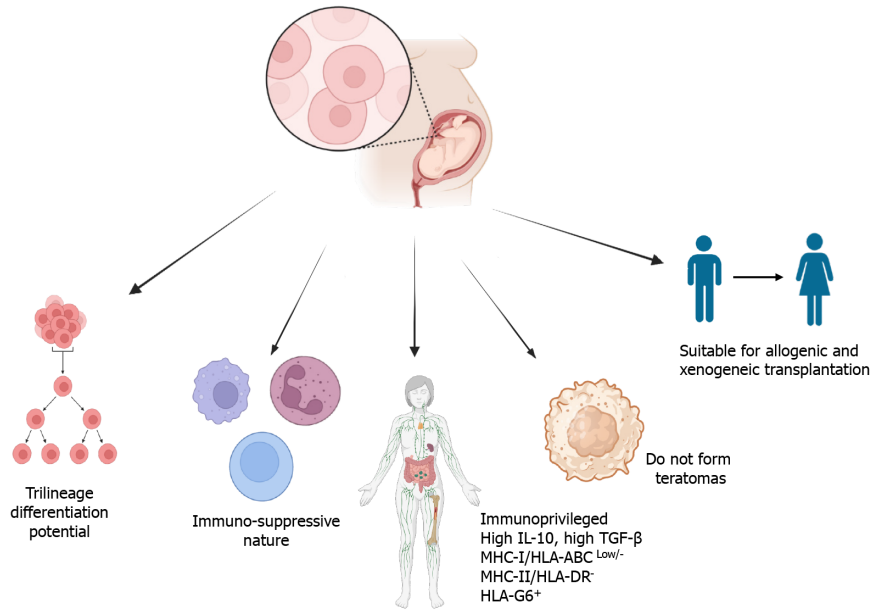

Figure 3 Properties of Wharton's jelly mesenchymal stem cells. Wharton's jelly mesenchymal stem cells possess trilineage differentiation potential, making them multipotent. They are immune-suppressive, immunoprivileged, and non-tumorigenic, ideal for allogeneic and xenogeneic transplantation due to their favorable properties (created with BioRender.com). IL: Interleukin; MHC: Major histocompatibility class; TGF: Transforming growth factor.

growth factor (HGF), galectin-1, and HLA-G5, which are effective factors for immunosuppression[47-49]. The secretion of inhibitory cytokines such as IL-10, IL-6, IL-8, TGF-β2, and HGF inhibits T helper type 17 (Th17) cells and stimulates regulatory T (Tregs) cells. It inhibits the proliferation of activated T cells by secreting IDO and PGE2 and upregulates the expression of programmed death ligand 1[50-52]. WJ-MSCs can suppress allogenic-stimulated immune cells to a greater extent than either BM-MSCs or adipose-derived MSCs (AD-MSCs)[25]. WJ-MSCs infusion more effectively decreased the incidence and severity of graft-*vs*-host disease (GvHD) compared to human decidua mesenchymal stromal cells, hBM-MSCs, and human adipose-derived stem cells, which was mediated by the enrichment of myeloid-derived suppressor cells in GvHD target tissues[53]. hUC-MSC- extracellular vesicles are reported to prevent life-threatening acute GvHD by modulating immune responses[54]. In addition to immunomodulation, they have applications in regenerative medicine

and tissue engineering.

Regenerative potential of WJ-MSCs

Because of their primitive nature, immuno-privileged status, and inexhaustible source of stem cells, WJ-MSCs have greater potential in clinics for regenerative medicine. WJ-MSCs produce abundant amounts of tissue growth-promoting factors such as VEGF, granulocyte-colony stimulating factor (G-CSF), platelet-derived growth factor, TGF-β, IL-6, IL-8, and insulin-like growth factor-1 (IGF1)[35,39,45]. These unique features of WJ-MSCs make them an excellent alternative source of MSCs for allogeneic transplantation to repair and regenerate different organs and tissues, including skin, heart, fat, cartilage, bone, pancreas, neural and vascular/endothelial constituents[31,46,55-57], as well as xenogeneic transplantations to improve organ function *in vivo*[56,58] in regenerative medicine (Figure 4). Functional regeneration of lung[59], kidney[60], and liver[61] tissues using human WJ-MSCs has been shown to be associated with reduced fibrosis and improved growth of functional parenchyma and normal stroma. WJ-MSCs may also promote skin regeneration by differentiating into different types of epithelial cells found in the sweat glands[62]. Nilforoushzadeh *et al*[63] have shown that subcutaneous infusion of WJ-MSCs in diabetic wounds has improved the density of new epidermis, dermis, and skin elasticity in the healed region of the wound, effectively accelerating healing. The presence of human fibroblast growth factor, hHGF, hG-CSF, hIL-1Rα, hVEGF, and hIL-6 in the secretome may elucidate the regenerative potential of the xeno-free cell-based and cell-free approaches, which have translational value for advanced wound care. The results reveal the therapeutic potential of both the cell-based and cell-free approaches for wound healing[64].

In diseases like Parkinson's disease, motor activities, the number of dopaminergic neurons, and levels of dopamine and tyrosine hydroxylase activities are reduced. WJ-MSCs have shown beneficial effects in improving the dopaminergic cells in Parkinson's disease. Jalali *et al*[65] have shown that infusion of WJ-MSCs along with L-dopa/carbidopa improved their levels. Chronic treatment with WJ-MSCs, alone and in combination with L-Dopa, improved nociception and cognitive deficit in Parkinson's disease rats, which may be the result of increasing IGF-1 and protecting the viability of dopaminergic neurons[66,67]. WJ-MSCs were readily differentiated into WJ Schwann cell-like cells, which effectively promoted the regeneration of peripheral nerves. Transplantation of WJ Schwann cell-like cells with acellular nerve grafts might be useful for assisting peripheral nerve regeneration[68].

Preclinical studies were conducted in a trinitrobenzene sulfonic acid-induced colitis animal model for hUC-MSCs, and it was observed that systemic infusion of hUC-MSCs could home to the inflamed colon and effectively ameliorate colitis [69]. In addition to the known suppressive effects on Th1-type immune responses, hUC-MSC-mediated modulation of IL-23/IL-17 regulated inflammatory reactions also plays an important role in the amelioration of colitis[69]. In another study, Chao *et al*[70] have shown that hUC-MSCs protected against experimental colitis by boosting the numbers of CD5 + B cells and IL-10-producing CD5 + Bregs and correcting Treg/Th17/Th1 imbalances. In a randomized controlled clinical trial, after UC-MSC infusion, steroid dosage significantly decreased, and the Crohn's disease (CD) patients' conditions also improved significantly. This indicates that UC-MSCs can attenuate immune malfunction in patients with CD. UC-MSCs therapy can significantly and safely improve the disease condition in patients with CD receiving a stable steroid dose[71]. A clinical trial for the use of WJ-MSCs in inflammatory bowel disease was started but it resulted in not being available (https://clinicaltrials.gov/ct2/show/NCT03299413).

WJ-MSC-derived extracellular vesicles have the potential to reduce cytokine storm reactions in patients with both chronic inflammatory diseases and viral infections[72]. Cytokine storm is recognized as one of the factors contributing to organ failure and mortality in patients with coronavirus disease 2019 (COVID-19). Therefore, a study was conducted on five patients with severe COVID-19 who were treated with WJ-MSCs (150×10^6 cells per injection). It was found that the levels of IL-10 and stromal cell-derived factor-1 increased after cell therapy, while the levels of VEGF, TGF-β, IFN-γ, IL-6, and tumor necrosis factor (TNF)-α decreased[73].

WJ-MSCs exhibit significant regenerative potential, making them a promising option for various therapeutic applications. However, it is essential to consider their weaknesses to provide a balanced view. One major issue is the heterogeneity of WJ-MSCs, with considerable variability between donors and even between different batches from the same donor[74]. This variability complicates the standardization of cell-based therapies, making it difficult to optimize cell staging, dosages, and delivery methods, which can lead to inconsistencies in effectiveness and efficiency[75]. Additionally, long-term safety concerns such as potential tumorigenicity and unwanted immune responses require thorough evaluation[76]. The lack of standardized protocols for the isolation, expansion, and application of WJ-MSCs further complicates regulatory approval and clinical implementation. Addressing these challenges through continued research and technological advancements is crucial for unlocking the full therapeutic potential of WJ-MSCs.

Safety and doses of WJ-MSCs

Despite their potential therapeutic benefits, MSCs are hindered by concerns over their potential to promote cancer. Studies have shown that MSCs can support the stem cell phenotype of acute myeloid leukemia and protect acute promyelocytic leukemia cells from apoptosis[76]. Additionally, MSCs have been implicated in promoting cancer progression by inducing epithelial to mesenchymal transition, enhancing cancer cell migration, and increasing tumor growth and metastasis[76]. The specific mechanisms behind these cancer-promoting characteristics of MSCs remain unclear, highlighting significant obstacles to their adoption in cancer therapies. As for WJ-MSCs, they are an ideal candidate for regenerative medicine, not only because they have huge regenerative potential but also because they have been reported to be non-tumorigenic and even anti-tumorigenic, suggesting their safety for cancer therapy as well[77,78]. They have low immunogenicity and are not rejected by the host immune system[79,80]. The dosage or count of WJ-MSCs for infusion varies from 0.2×10^6/kg to 8.7×10^6/kg in various disease conditions. The cell counts to be administered are mostly calculated relative to body weight, although some clinical studies have also applied arbitrary counts[80]. Regarding WJ-MSC transplantation for diabetes mellitus, a dose of 1×10^6/kg has been reported several times.

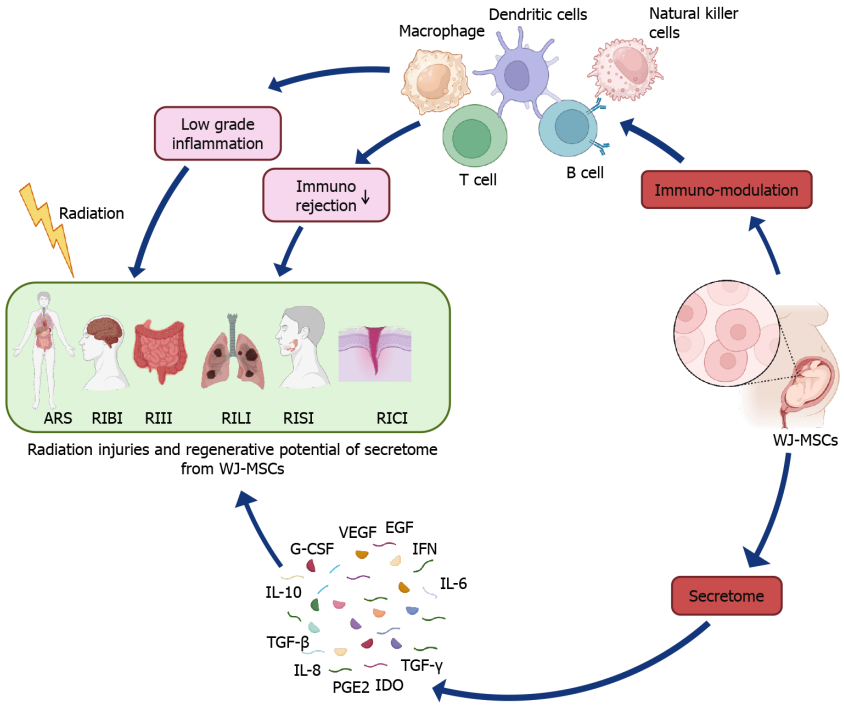

Figure 4 Illustration of multifaceted role of Wharton's jelly mesenchymal stem cells in mitigating radiation-induced injuries through direct and indirect immunoregulation. These cells expertly modulate key immune players: B-cells, macrophages, dendritic cells, and natural killer cells, maintaining controlled inflammation. Wharton's jelly mesenchymal stem cells (WJ-MSCs) engage in immune regulation *via* T-cell interactions, displaying HLA class I molecules while lacking costimulatory molecules, thus minimizing rejection risks. In inflamed environments, CD40 and HLA class II molecules may be expressed. WJ-MSCs' secretome is a potent source of regenerative factors. It contains prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), endothelial growth factor (EGF), vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-10, transforming growth factor (TGF)-β1, TGF-γ, GCSF, soluble HLA-G5, and soluble galectins (1, 3, and 9). Additionally, WJ-MSCs express indoleamine-2,3-dioxygenase (IDO), driving tryptophan depletion in the medium and generating tryptophan metabolites (kynurenine, 3-hydroxykynurenine, and kynurenic acid). This intricate web of immunomodulation and soluble factors highlights WJ-MSCs' therapeutic potential in radiation injury recovery (created with BioRender.com). IFN: Interferon; ARS: Acute radiation syndromes; RIBI: Radiation-induced brain injury; RICI: Radiation-induced cutaneous injury; RIII: Radiation-induced intestinal injury; RILI: Radiation-induced lung injury; RISI: Radiation-induced salivary gland injury.

RADIATION INJURIES AND REGENERATIVE POTENTIAL OF WJ-MSCs

The molecular mechanisms underlying radiation injuries and their repair are complex, involving DNA damage, oxidative stress, and inflammatory responses (Figure 5). Better understanding of these mechanisms is crucial for leveraging the therapeutic potential of WJ-MSCs. These cells help mitigate radiation injury through paracrine signaling, immunomodulation, differentiation, and direct cell-to-cell interactions[81]. Ionizing radiation causes DNA damage, including single-strand and double-strand breaks, potentially leading to mutations and cell death[11]. WJ-MSCs exhibit strong DNA repair capabilities and secrete growth factors like HGF and IGF-1[82]. However, their ability to enhance DNA repair in neighboring cells requires further investigation. Radiation also generates reactive oxygen species (ROS), causing oxidative damage and impairing mitochondrial function. WJ-MSCs release antioxidant enzymes such as superoxide dismutase and catalase, which neutralize ROS[83]. Studies have shown that WJ-MSCs' protective effects against oxidative stress involve paracrine signaling and extracellular vesicle release[83]. They express crucial ROS-managing enzymes[84] and can transfer healthy mitochondria to damaged cells *via* tunneling nanotubes, restoring mitochondrial function[85]. Additionally, radiation induces pro-inflammatory cytokines, leading to sustained inflammation and tissue damage[86]. WJ-MSCs migrate to injury sites using chemokine receptors and adhesion molecules, secreting radioprotective and tissue-regenerative factors to modulate the immune response[12]. They regulate immunity through cell-cell contact with T cells and produce soluble factors (PGE2, HGF, IL-6, IL-10, TGFβ1) that reduce T-cell proliferation, induce T-cell apoptosis, and promote regulatory T cells, thereby mitigating radiation-induced inflammation and promoting tissue regeneration[83]. During RT for cancer, damage to normal tissues near the tumor can occur, leading to the development of xerostomia in head and neck cancer, lung fibrosis in lung cancer, or enteritis/colitis in colon and pelvic cancer. These limitations compromise the therapeutic outcome of RT. Emerging studies using stem cells suggest that the infusion of WJ-MSCs could be beneficial in managing several of these RT complications (Figure 6). WJ-MSCs have shown significant potential in mitigating acute and late radiation side effects due to their anti-inflammatory, antioxidant, and regenerative properties. These cells can be administered early after RT or to treat established late effects by inhibiting fibrosis, enhancing vascular regeneration, and reducing chronic inflammation[87]. The potential of WJ-MSCs in managing radiation enteropathy, a common side effect of abdominal and pelvic RT, is also being explored[88].

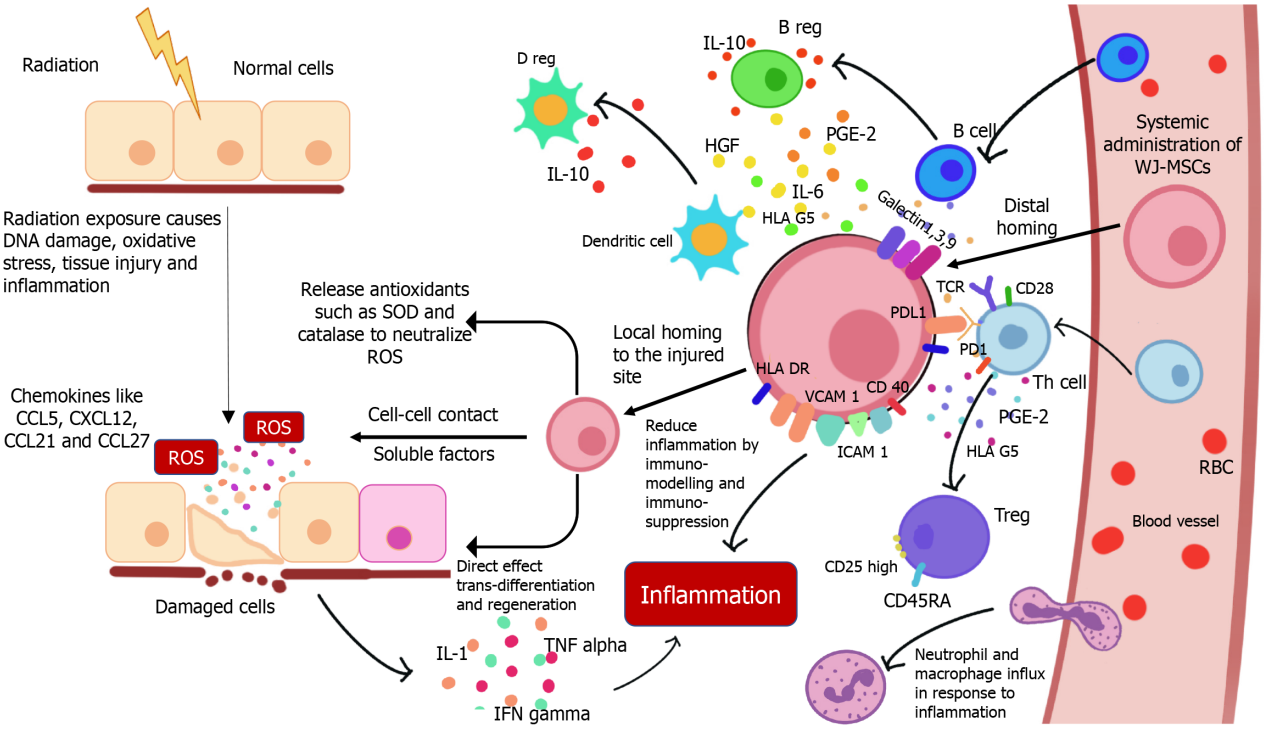

Figure 5 Molecular mechanism of tissue repair and regeneration by Wharton's jelly mesenchymal stem cells. Radiation-induced reactive oxygen species (ROS) causes cellular damage. In response to Wharton's jelly, mesenchymal stem cells (WJ-MSCs) release antioxidant enzymes [superoxide dismutase (SOD), catalase] and transfer healthy mitochondria to damaged cells. Radiation triggers the release of pro-inflammatory cytokines [*e.g.*, tumor necrosis factor-α, interleukin (IL)-1β, interferon (IFN)-γ], causing inflammation and tissue damage. WJ-MSCs migrate to injury sites, guided by chemokine receptors and adhesion molecules. WJ-MSCs interact with T cells through cell-cell contact and soluble factors, inhibiting T-cell proliferation, inducing T-cell apoptosis, and promoting the formation of regulatory T cells. They also secrete factors like prostaglandin E2 (PGE2), hepatocyte growth factor (HGF), IL-6, IL-10, transforming growth factor (TGF) β1, soluble human leukocyte antigen (HLA)-G5, and soluble galectins (1, 3, 9), which help modulate the immune response. Additionally, WJ-MSCs prevent dendritic cell maturation, altering natural killer and B cell functions to reduce inflammation and support tissue repair. Breg: B regulatory cell; CD: Cluster of differentiation; D reg: Dendritic regulatory cell; ICAM: Intercellular adhesion molecule; PD1: Programmed death 1; PDL1: Programmed death-ligand 1; RBC: Red blood cell; TCR: T cell receptor; Th cell: T helper cell; Tregs: T regulatory cells; VCAM: Vascular cell adhesion molecule; VEGF: Vascular endothelial growth factor.

Acute radiation syndromes

Acute radiation syndromes (ARS), also known as triple syndrome (comprising hematopoietic, gastrointestinal, and central nervous syndromes), can develop after whole-body radiation exposure, either knowingly (such as in RT, reactor maintenance, or clean-up) or unknowingly (due to radiation accidents). Zhang *et al*[89] have demonstrated the beneficial role of umbilical cord blood stem cell transplantation in the recovery of hematopoietic syndrome in experimental mice. Kovalenko *et al*[90] have shown that the administration of 2×10^8 human umbilical cord blood mononucleated cells within 24-52 hours following irradiation, along with the antibiotic levaquin, significantly enhances the probability of survival compared to irradiated and untreated animals. Very recently, Bandekar *et al*[35] showed that therapeutic infusion of WJ-MSCs after lethal exposure to radiation (8.5 Gy) reduces the symptoms of ARS. WJ-MSCs have the capability to preferentially home into radiosensitive tissues like the spleen, bone marrow, and small intestine of irradiated mice, and secrete various soluble mediators while minimizing radiation toxicity[35]. However, the infusion of WJ-MSCs in normal mice results in their random distribution[91]. The transplanted xenogeneic WJ-MSCs produce human cytokines and enhance the production of mouse cytokines in irradiated mice. Among these, WJ-MSC-derived human IL-6 and G-CSF were found to play a causal role in radioprotection[35,92].

Radiation-induced cutaneous injury

Radiation-induced cutaneous injury, also known as radiation dermatitis, manifests due to repeated exposure to radiation on the skin during RT. The skin is the first organ to come into contact with external RT, making it the most common type of radiation injury. It limits the duration and dose of radiation that can be delivered to the patient. Sun *et al*[93] showed that the orthotropic application of WJ-MSCs-derived conditioned media significantly increases the wound-healing rate by effectively promoting tissue repair and regeneration in radiation-damaged skin in rats, signifying the role of WJ-MSCs in acute radiation skin injury. The regenerative mechanism mediated by WJ-MSC-conditioned medium (CM) involves tissue regeneration due to the presence of secreted soluble factors that reduce inflammation, enhance alpha-smooth muscle actin expression, and promote angiogenesis, thereby increasing the total number of vessels in the healed wound skin[94]. Additionally, the CM from WJ-MSCs also accelerates scar-free wound healing. These findings point towards an urgent need for optimization and benchmarking of the method of isolation and preservation of conditioned media from WJ-MSCs for possible use as a therapeutic agent for the treatment of radiation-induced dermatitis[93].

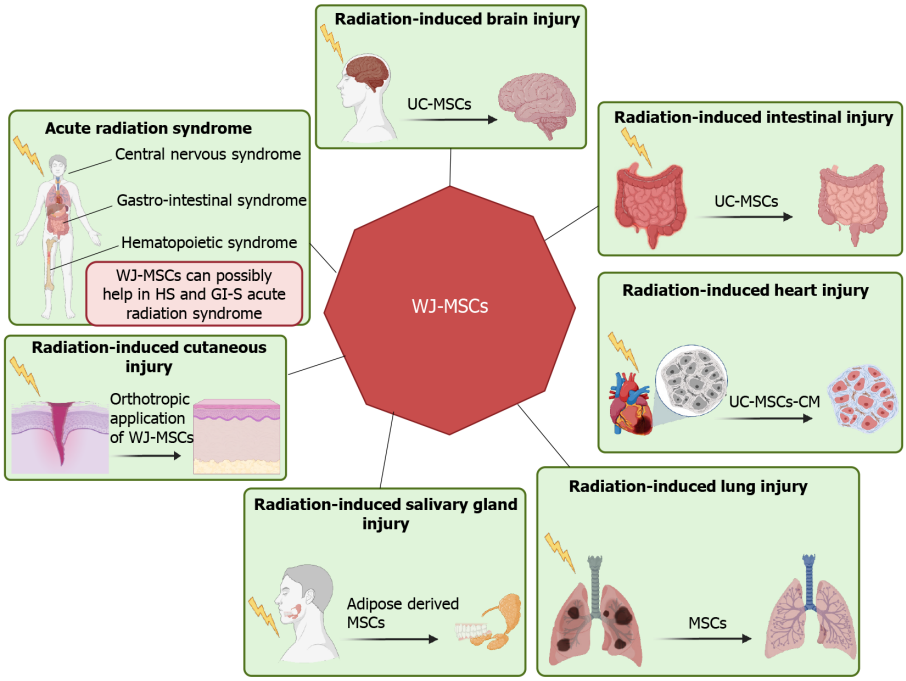

Figure 6 Diagrammatic illustration showing regenerative potential of Wharton's jelly mesenchymal stem cells in various radiation injuries. Created with BioRender.com. WJ-MSCs: Wharton's jelly mesenchymal stem cells; UC-MSC: Umbilical cord mesenchymal stem cell; CM: Conditioned media; HS: Hematopoietic syndrome; GI-S: Gastrointestinal syndrome.

Radiation-induced salivary gland injury

During RT for head and neck cancer, the salivary glands are inevitably exposed to radiation, resulting in severe damage and the development of radiation-induced salivary gland injury (RISI). After undergoing RT for head and neck cancer, most patients experience xerostomia, dysphagia, dental caries, and other issues that negatively impact their social and professional lives. This is due to the irreversible loss of acinar cells, sterilization of primitive glandular stem cells, and decreased saliva secretion (known as hyposalivation) caused by radiation exposure, respectively[95]. In the early stages of exposure, there are no morphological changes, but saliva secretion diminishes, possibly due to cell membrane damage caused by radiation-induced ROS or alterations in signaling pathways and ion channels such as Aqp5[96]. However, in the later stages, significant morphological changes occur, including atrophy and loss of acinar cells, duct dilation, and infiltration of chronic inflammatory cells[97]. Until now, neither the prophylactic use of amifostine (to prevent radiation-induced xerostomia)[98] nor symptomatic treatment strategies (such as pilocarpine, which stimulates saliva secretion) have provided satisfactory relief from symptoms. However, IMRT has been shown to be effective in reducing the dose delivered to the parotid glands, thus potentially reducing the risk of parotid gland injury[99]. Because radiation-induced xerostomia results from the loss of stem cells, the infusion of stem cells may aid in the regeneration of salivary glands. There have been reports on the use of adult tissue stem cells, such as HSCs, MSCs, and salivary stem/progenitor cells, for rescuing radiation-induced xerostomia.

Although there is currently no report on the effect of WJ-MSCs on RISI, other sources of stem cells have shown beneficial effects, and the same is expected for WJ-MSCs. Schwarz *et al*[100] demonstrated that intra-glandular infusion of BM-MSCs was retained in inflamed glands, while intravenous infusion reached both normal and damaged submandibular glands. Xiong *et al*[101] showed that transplantation of AD-MSCs was beneficial in alleviating xerostomia, possibly by aiding in the regeneration of salivary glands after intra-glandular transplantation. They observed that the transplanted AD-MSCs survived and differentiated into salivary epithelial cells.

Radiation-induced lung injury

RT is one of the key treatment modalities for thoracic cancers such as lymphoma, lung, breast, and esophageal cancer. Radiation-induced lung injury (RILI) develops post-RT due to severe cell damage after repeated radiation exposure. Manifestations of RILI include early-stage radiation pneumonitis (1-6 months after RT) and late-stage pulmonary fibrosis (1-2 years after RT). Although high-dose steroids can effectively treat acute radiation pneumonitis, there is currently no approved causative treatment for late-onset pulmonary radiation damage such as pulmonary fibrosis[87]. Radiation exposure results in an increase in reactive oxygen and nitrogen levels in epithelial and endothelial cells, causing damage. These damaged cells start producing pro-inflammatory cytokines, which alter vasodilation and vascular permeability and recruit cells of the immune system, resulting in chronic inflammation. These damages lead to the loss of epithelial and endothelial cells, causing blood-air dysfunction and increased vascular permeability. In the late stage, they ultimately develop fibrosis. The development of fibrosis causes damage to tissue architecture, which interferes with gaseous exchange, resulting in dyspnea, accumulation of fluid in the interstitial space, and ultimately respiratory failure and death. Despite significant advancements in the safety of RT, on average, 10%-30% of patients develop symptoms of RILI

after thoracic RT[102]. RILI not only affects the quality of life of the patients but also increases the chances of death. Until now, apart from amifostine, we do not have any other treatment regimens for it. In the last few decades, cell-based therapy employing MSCs has played a significant role in reducing lung fibrosis by promoting the repair of damaged tissue as well as secreting anti-inflammatory mediators and anti-fibrotic factors. They are also known to suppress T-cell activity and reduce B-cell activation and proliferation. Under inflammatory conditions, MSCs secrete IDO, PGE2, and IL-10, which have a regulatory function.

Hao *et al*[103] showed that intratracheal transplantation of UC-MSCs in a canine model reduced oxidative stress, inflammatory reactions, and TGF-β-Smad2/3 pathways, thereby reducing RILI. Zhang *et al*[104] reported that CXCR4-overexpressing WJ-MSCs preferentially home to damaged lung tissues and show improved therapeutic potential for the treatment of RILI. The protection offered by WJ-MSCs was associated with a reduction of radiation-induced increase in stromal cell-derived factor-1, TGF-β1, alpha-smooth muscle actin, and collagen I levels, as well as a protection from radiation-induced decrease in the expression of E-cadherin, leading to the moderation of RILI.

Radiation-induced heart injury

During thoracic exposure to radiation, heart injury is also associated with lung injury. Radiation causes fibrosis in all components of the heart and significantly increases the risk of coronary artery disease, cardiomyopathy, valvulopathy, arrhythmias, and pericardial disease[105]. Heart injury comprises myocardial, coronary artery, pericardial, valvular, and conduction system diseases, which have been observed in breast cancer and Hodgkin's lymphoma patients[106-108]. Chen *et al*[109] assessed the therapeutic effect of human UC-MSCs-CM on radiation-induced myocardial fibrosis. They found that irradiated human cardiac fibroblasts cultured with UC-MSCs-CM showed greater viability. Inhibited nuclear factor-kappa B activity decreased the expression of several pro-fibrotic cytokines, including TGF-β1, IL-6, and IL-8, followed by mitigated collagen deposition and fibrosis. Meanwhile, changes in oxidation markers (malondialdehyde) and antioxidant enzyme levels reflected reduced oxidative stress[109]. However, specific nutritional factors released by MSCs that are involved in myocardial protection from ionizing radiation were not clarified[109].

Radiation-induced intestinal injury

During RT for abdominal and pelvic cancers, exposure of radiation to the intestine is unavoidable. This radiation exposure causes serious damage to intestinal villi, leading to mucosal erosion, intestinal vascular permeabilization, chronic inflammation, and eventually developing into radiation enteritis/proctitis/colitis, intestinal ischemia, mucositis, ulcers, necrosis, or even perforation. The development of these conditions after RT worsens the quality of life of these patients. Depending on the total dose of RT, size of the radiation field, course time, and division method, radiation enteritis can be divided into acute phase and chronic phase[20,23]. Acute radiation enteritis occurs within 1-2 weeks and is characterized by main manifestations such as nausea, emesis, stomachache, acute diarrhea, and tenesmus. On the other hand, chronic radiation enteritis generally occurs after several months or years and is characterized mucous bloody stool, intestinal stenosis, anal pendant expansion, and even intestinal obstruction. Bandekar *et al*[35] have shown that infusion of WJ-MSCs helps in the recovery of Lgr5 + stem cells in mice.

Radiation-induced brain injury

This is one of the most common types of injury that takes place during RT for head and neck cancer. It involves damage to the cerebral-vascular system, inflammatory response, and oxidative stress in the brain, which causes progressive cognitive dysfunction. Radiation exposure to the brain depletes the neuronal stem/precursor cell pools primarily residing in the neurogenic region of the hippocampus, leading to cognitive deficits. Therefore, transplantation of stem cells may be a promising option for restoring cognitive function in the brain. Very recently, Wang *et al*[110] have shown that infusion of UC-MSCs to 15 Gy whole body irradiated mice inhibits brain injury and imparts a neuroprotective effect. It inhibits neuro-inflammation by decreasing the levels of the inflammatory cytokines (TNF-α and IL-6) and increasing the level of IL-10, significantly improving the learning and memory of the mice. These studies demonstrated profound beneficial effects of either ESCs or neuronal stem cells (derived from iPSCs) in ameliorating the adverse effects of radiation on the brain in a preclinical rat model[111,112].

CLINICAL TRIALS OF WJ-MSCs IN REGENERATIVE MEDICINE

The first clinical trial to test the feasibility and efficacy of WJ-MSC therapy was registered in 2008. By May 2024, the public clinical trials database, https://www.clinicaltrials.gov/, had shown 48 clinical trials using WJ-MSCs for a wide range of therapeutic applications (Table 3, keywords used: "Wharton's jelly mesenchymal stem cells" or "umbilical cord mesenchymal stem cells"). Most of these trials are safety studies (phase I) and proof of concept (phase II), with very few in phase III (comparison of a new treatment to the standard treatment).

FUTURE APPLICATIONS AND PERSPECTIVE

The pre-clinical observations of WJ-MSCs for mitigating radiation injuries show its significant potential in managing the side effects of RT. The future application of WJ-MSCs in treating radiation injuries is promising, with several novel techniques emerging. Enhanced delivery technologies like nanotechnology, hydrogels, and microencapsulation are key

Table 3 List of clinical trials using Wharton's jelly mesenchymal stem cells for it therapeutic applications

No.	Study title	Clinical trial code numbers	Conditions	Status/conclusions
1	Randomized study of coronary revascularization surgery with injection of WJ-MSCs and placement of an epicardial extracellular matrix	NCT04011059	Cardiovascular diseases: Heart failure, coronary artery disease Mesenchymal stem cell transplantation, regenerative medicine	Not yet recruiting
2	MSCs for prevention of MI-induced HF	NCT05043610	Myocardial infarction: Acute, anterior wall Cardiac remodeling, ventricular STEMI, regenerative medicine Heart failure	Recruiting
3	The application of the umbilical cord mesenchymal stem cells in the complex treatment of non-ischemic heart failure	NCT04325594	Chronic heart failure Non-ischemic cardiomyopathy, dilated cardiomyopathy	Completed. Result not available
4	Treatment of degenerative disc disease with allogenic mesenchymal stem cells (MSV)	NCT01860417	Degenerative disc disease Intervertebral disc disease Low back pain	Completed. Result available. But not concluded yet
5	Treatment of knee osteoarthritis with allogenic mesenchymal stem cells	NCT01586312	Arthritis of knee	Completed. Result available. But not concluded yet
6	Ultrasound-guided treatments for shoulder pain in wheelchair users with spinal cord injury	NCT04136743	Spinal cord injuries Tendinopathy Rotator cuff tears Shoulder pain	Recruiting
7	Ultrasound-guided injections for meniscal injuries in active-duty military	NCT04274543	Tibial meniscus injuries Knee injuries and disorders	Recruiting
8	3D tissue engineered bone equivalent for treatment of traumatic bone defects	NCT03103295	Bone defects	Unknown status
9	Safety and feasibility study of the CELLSPAN esophageal implant (CEI) in patients requiring short segment esophageal replacement	NCT05877300	Esophageal diseases	Not yet recruiting
10	Micro-fragmented adipose tissue and complex Crohns' anal fistulas	NCT03555773	Crohn disease, perianal fistula	Completed. Result not available
11	Micro-fragmented adipose Tissue (LipogemsÂ®) injection for chronic shoulder pain in persons with spinal cord injury	NCT03167138	Shoulder pain Shoulder impingement syndrome Rotator cuff impingement syndrome, rotator cuff tendinitis, rotator cuff syndrome of shoulder and allied disorders Spinal cord injuries	Unknown status
12	Encapsulated mesenchymal stem cells for dental pulp regeneration	NCT03102879	Periapical periodontitis	Completed. Result available. But no conclusion
13	Allogeneic cord blood cells for adults with severe acute contusion spinal cord injury	NCT04331405	Spinal cord contusion	Completed. Result not available
14	Wharton's jelly-derived mesenchymal stem cells in osteoarthritis	NCT03866330	Osteoarthritis: Hip, knee, glenohumeral	Unknown status
15	Cardiovascular clinical project to evaluate the regenerative capacity of cardiocell in patients with acute myocardial infarction (AMI)	NCT03404063	Myocardial infarction	Completed. Result not available
16	Randomized clinical trial to evaluate the	NCT03418233	Heart failure	Completed. Result not

	regenerative capacity of cardiocell in patients with chronic ischaemic heart failure (CIHF)			available
17	Cardiovascular clinical project to evaluate the regenerative capacity of cardiocell in patients with no-option critical limb ischemia (N-O CLI)	NCT03423732	Critical limb ischemia	Unknown status
18	Transplantation of allogeneic MSC in patients with pulp necrosis and chronic apical periodontitis	NCT04545307	Pulp Necroses | Apical Periodontitis	Completed. Result not available
19	Efficacy of intradiscal injection of autologous bm-MSC in subjects with chronic LBP due to multilevel lumbar IDD	NCT05066334	Intervertebral Disc Degeneration | Chronic Low-back pain	Recruiting
20	Allogeneic ADSCs and platelet-poor plasma fibrin hydrogel to treat the patients with burn wounds (ADSCs-BWs)	NCT03113747	Second- or third-degree burns	Unknown status
21	Allogeneic mesenchymal stromal cells in elderly patients with hip fracture	NCT02630836	Femoral neck fracture	Withdrawn
22	Umbilical cord blood-derived mesenchymal stem cells in regeneration of sweat glands and body repair	NCT02304562	Sweat gland diseases	Unknown status
23	Residual dental pulp tissue and cord blood stem cells	NCT04040127	Irreversible pulpitis	Withdrawn
24	Treatment of osteoarthritic knee with high tibial osteotomy and implantation of allogenic human umbilical cord blood-derived stem cells	NCT04234412	Osteoarthritis, knee	Unknown status
25	Umbilical cord blood collection and processing for hypoplastic left heart syndrome patients	NCT01856049	Hypoplastic left heart syndrome	Recruiting
26	Stem cell educator therapy in type 1 diabetes	NCT03390231	Type 1 diabetes	Unknown status
27	Use of Wharton Jelly in diabetic nephropathy	NCT03288571	Diabetic nephropathies	Not yet recruiting
28	Efficacy of Wharton jelly in erectile dysfunction	NCT03751735	Erectile dysfunction associated with type 2 diabetes mellitus	Completed. Result not available
29	Safety of Wharton Jelly in erectile dysfunction	NCT02945449	Erectile dysfunction associated with type 2 diabetes mellitus	Completed. Result not available
30	Treatment of COVID-19 patients using Wharton's jelly-mesenchymal stem cells	NCT04313322	Use of stem cells for COVID-19 treatment	Recruiting
31	Use of mesenchymal stem cells in inflammatory bowel disease	NCT03299413	Inflammatory bowel diseases	Active, not recruiting
32	Intrathecal administration of expanded Wharton's jelly mesenchymal stem cells in chronic traumatic spinal cord injury	NCT03003364	Spinal cord injury, chronic	Completed. Result not available
33	Evaluation of umbilical cord-derived Wharton's jelly stem cells for the treatment of acute graft *versus* host disease	NCT03158896	Acute graft *versus* host disease	Active, not recruiting
34	Use of Wharton Jelly-derived mesenchymal stem cells for knee osteoarthrosis	NCT02963727	Knee osteoarthrosis	Recruiting
35	Management of retinitis pigmentosa by Wharton's jelly-derived mesenchymal stem cells	SHGM56733164	Retinitis pigmentosa Inherited retinal dystrophy	Completed. Result not available
36	Safety and efficacy of intravenous Wharton's jelly-derived mesenchymal stem cells in acute respiratory distress syndrome due to COVID-19	NCT04625738	Acute respiratory distress syndrome	Not yet recruiting
37	Wharton's jelly-derived mesenchymal stem cells in osteoarthritis	NCT03866330	Osteoarthritis: Hip, knee, glenohumeral	Recruiting
38	Intracoronary human Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) transfer in patients with acute myocardial infarction (AMI)	NCT01291329	ST-elevation myocardial infarction	Completed. Result not available

39	Therapeutic potential of stem cell conditioned medium on chronic ulcer wounds	NCT04134676	Chronic ulcer	Not yet recruiting
40	Effect of implanting allogenic cytokines derived from human amniotic membrane (HAM) and mesenchymal stem cells derived from human umbilical cord Wharton's jelly (HUMCWJ) on pain and functioning of knee osteoarthritis	NCT03337243	Knee osteoarthritis Knee pain chronic Joint disease Musculoskeletal disease	Completed. Result not available
41	Intracoronary or intravenous infusion human Wharton's jelly-derived mesenchymal stem cells in patients with ischemic cardiomyopathy	NCT02368587	Ischemic cardiomyopathy	Not yet recruiting
42	Therapeutic treatment of amyotrophic lateral sclerosis	NCT02881476	Amyotrophic lateral sclerosis	Unknown
43	Pericardial matrix with mesenchymal stem cells for the treatment of patients with infarcted myocardial tissue	NCT03798353	Myocardial infarction	Recruiting
44	A research study looking at specific tissue of the umbilical cord	NCT01166776	Varices of umbilical cord	Completed. Result not available
45	Efficacy and safety evaluation of mesenchymal stem cells for the treatment of patients with respiratory distress due to COVID-19	NCT04390139	COVID-19, SARS-CoV-2 Adult respiratory distress syndrome	Recruiting
46	Treatment of spinal cord injuries with (AutoBM-MSCs) *versus* (WJ-MSCs)	NCT04288934	Spinal cord injuries	Recruiting
47	Cell therapy using umbilical cord-derived mesenchymal stromal cells in SARS-CoV-2-related ARDS	NCT04333368	SARS-CoV-2 Severe acute respiratory distress syndrome	Recruiting
48	Role of stem cells in improving implantation rates in ICSI patients	NCT01649752	Assess the efficacy of differentiated and undifferentiated stem cell therapy in improving endometrial receptivity	Unknown
49	Wharton's jelly-derived mesenchymal stromal cell repeated treatment of adult patients diagnosed with type I diabetes	NCT03973827	Type 1 diabetes	Recruiting

WJ-MSCs: Wharton's jelly mesenchymal stem cells; MSC: Mesenchymal stem cell; MI: Myocardial infarction; HF: Heart failure; CEI: CELLSPAN esophageal implant; AMI: Acute myocardial infarction; CHF: Chronic heart failure; CLI: Critical limb ischemia; BM-MSC: Bone marrow mesenchymal stem cell; LBP: Low back pain; IDD: Intervertebral disc degeneration; ADSC: Adipose-derived stem cell; ADSC-BW: Adipose-derived stem cell-burn wound; COVID-19: Coronavirus disease 2019; HAM: Human amniotic membrane; HUMCWJ: Human umbilical cord Wharton's jelly; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; ICSI: Intracytoplasmic sperm injection.

areas of focus. Nanoparticles and nanocarriers can protect cells during transit and deliver them precisely to damaged sites, while hydrogels offer a supportive matrix for improved cell retention and function. Microencapsulation enhances the therapeutic effectiveness of WJ-MSCs by protecting them. Personalized medicine aims to tailor WJ-MSCs treatments based on a patient's genetic profile and specific injury characteristics, potentially improving outcomes. Genetic manipulation of WJ-MSCs to express higher levels of therapeutic factors such as VEGF can enhance their regenerative potential. Increasing their resistance to apoptosis can also improve their survival and efficacy in the hostile post-radiation environment. Further research into WJ-MSCs' ability to repair DNA in damaged cells can reveal mechanisms to minimize radiation harm and enable genetic modifications for more effective regeneration. Combining WJ-MSC's therapy with other treatments, such as antioxidants or anti-inflammatory agents, can amplify healing effects. Pharmaceutical agents that enhance MSCs homing and engraftment, like CXCR4 agonists and heparin, are also promising. Thus, future strategies to enhance the therapeutic potential of WJ-MSCs involve genetic modification, preconditioning of MSCs, rigorous screening, advancing research to fully understand their mechanisms of action, and standardized production and enhanced delivery techniques. Personalized treatment protocols, harmonizing regulatory guidelines, and developing innovative delivery systems are essential steps. Several challenges still need to be addressed before transferring WJ-MSCs from the bench to the bedside. These challenges include: Do WJ-MSCs remain immuno-privileged and maintain their hypo-immunogenicity and paracrine properties after differentiation? What will be their post-transplantation status? How much cell count/dose and post-RT time should be selected for desired benefits? Robust clinical trials with long-term follow-up are crucial to fully realize the therapeutic potential of WJ-MSCs in mitigating radiation injuries.

CONCLUSION

In conclusion, there are different sources of MSCs, and each has its own merits and demerits in terms of derivation, ethical issues, and safety for applications. Various pieces of evidence show that WJ-MSCs do not impose any ethical concerns, risk of forming teratomas, or immunorejection, which exist with BM-MSCs, ESCs, or iPSCs. Thus, WJ-MSCs-based therapy may offer an alternative to allogeneic bone marrow transplantation in accidental radiation exposure scenarios. Like other stem cells, WJ-MSCs also have limitations, such as different researchers following different isolation protocols. Therefore, clear guidelines, standardization and regulatory improvements are essential for widespread clinical adoption of WJ-MSCs. Owing to their unique properties, WJ-MSCs will be at the forefront of stem cell therapy for ameliorating radiation injuries developed after RT. We believe that in the future, more preclinical and clinical studies will be initiated to improve the quality of life for cancer patients who have undergone RT.

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