The application of human Wharton's jelly mesenchymal stem cells in wound healing: A narrative review

Reza Rezaee1, Javad Verdi2, Mahsa Sadeghi3, Mehran Soleymana4, Mojtaba Mirzaei5, Mohammad Reza Mobayen3, Arad Kianoush3,*

1Department of Healthcare Management, School of Management and Social Sciences, North Tehran Branch, Islamic Azad University, Tehran, Iran
2Department of Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
3Burn and Regenerative Medicine Research Center, Guilan University of Medical Sciences, Rasht, Iran
4Orthopedic Research Center; Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
5Yale New Haven Medical Center, Waterbury Hospital, Waterbury, Connecticut, United States

Abstract
Management and treatment of chronic wounds remain a significant problem in clinical practice. Stem cell therapies are an important and promising approach for regenerative medicine because of their self-renewal and differentiation potential. Mesenchymal stem cells (MSCs), a major cellular source for regeneration, are present in almost all tissues. The use of embryonic stem cells is morally controversial because of the need to nurture and destroy embryonic cells. Therefore, adult umbilical cord tissues are of particular importance as an alternative source of perinatal tissues. Wharton Jelly is a gelatinous connective tissue in the umbilical cord containing MSCs that can differentiate into osteogenic, adipose, chondrogenic, and other lineages. These cells do not express the MHC-II molecule and show immunomodulatory properties that make them viable for allogeneic and xenogenic transplants in cell therapy. Therefore, the umbilical cord, especially the part named Wharton’s jelly, is an important and promising source of mesenchymal stem cells.

Keywords: Stem cells, Wharton's Jelly, Cell therapy, Wound healing, Regenerative medicine

1. Introduction
Wounds are physical injuries caused by breakage of skin [1, 2]. Immediate and appropriate wound healing is essential for the re-establishment of functional tissues and the maintenance of structure following injury [3]. This complex and dynamic phenomenon involves cell-matrix interactions that heal wounds in three different overlapping phases, including the inflammatory, the proliferation, and the regenerative phase [4]. The naturally slow healing of wounds, rising costs, and inconsistency in healing are the most critical problems of this treatment. These problems have led to the discovery of more advanced therapies such as tissue engineering, gene therapy, platelet-rich plasma (PRP), the use of growth factors (GF) and stem cells (SC) [5]. Numerous studies have been performed using stem cells in different fields of diseases with promising results [6]. Cell therapy involves the replacement of stem cells or tissue made from stem cells for various disorders and injuries [7]. Stem cells are undifferentiated multifunctional cells that can differentiate into various types of cells.

*Corresponding author:
Arad Kianoush, MD
3rd floor of Velayat Hospital, Burn and Regenerative Medicine Research Center, Namjoo Street, Rasht, Guilan, Iran
Tel/Fax: +98 911 9295638/+98 13 33368540
Email: arad.kianoush@gmail.com
http://orcid.org/0000-0001-7184-054X

© The Author(s) 2022

Received: July, 26, 2021
Accepted: November, 20, 2021
cells are of embryonic or adult origin, depending on the type of tissue they are derived from [8]. Mesenchymal stem cells are a group of pluripotent, fibroblast-shaped mature stem cells that have the ability to self-renew, modulate the immune system, and differentiate into several cell lines [9, 10]. Although adult bone marrow is the most common source of mesenchymal stem cell extraction for clinical use, these cells can now be obtained from various tissues, including skin, adipose tissue, peripheral blood, umbilical cord (blood/Wharton jelly), endometrium, and tooth pulp [10-14]. In conditions of tissue damage, proinflammatory factors are usually produced by both innate and compatible immune responses. Studies have shown that in pathological conditions such as tissue damage, mesenchymal stem cells are inherently mobilized to the site of injury and are activated in an inflammatory environment in close interaction with the immune system [15]. These cells then facilitate wound healing by secreting specific cytokines and growth factors, increasing angiogenesis, inhibiting inflammation, increasing fibroblast migration, and collagen production [16]. In fact, the interactions between mesenchymal stem cells (MSCs) and inflammatory cells determine the outcome of tissue repair processes [15]. Today, mesenchymal stem cells isolated from extra-embryonic tissues such as umbilical cord Wharton's Jelly have been considered as a suitable cellular source [14, 17]. The reason for using these cells is easy and unlimited access, low cost, non-invasive in tissue isolation, the ability to differentiate into different cells, non-tumorigenic and abundant sources of these cells [10, 18]. Wharton's jelly is a mucous connective tissue surrounding umbilical arteries and veins covered by an amniotic epithelium. Umbilical cords are considered hospital waste, so their clinical application in research and cell therapy has no ethical concerns [19, 20]. Since the amount of Wharton jelly cells is limited and the amount of extracellular matrix (ECM) compounds is very high, it seems that its cells produce high amounts of collagen and glycosaminoglycans under the induction of existing growth factors [21]. Previous studies show that WJ-MSCs can be used for various diseases such as cancer, neurological disorders, kidney failure, and liver, lung, and orthopedic injuries. Recent advances show that WJ-MSCs reinforced with microparticles and scaffolds can be used more effectively for various clinical applications [22-28].

The advantage of WJ-derived mesenchymal stem cells over bone marrow-derived mesenchymal stem cells (BM-MSCs) and adipose tissue is that they do not express MHC-II. Moreover, these cells have stronger immunomodulatory properties due to the release of large amounts of anti-inflammatory molecules such as TGFβ, IL-10, IDO, TSG-6 and PGE2 [29-31]. Although, to date, there have been no reports of the use of human WJ-MSCs in human skin lesions, paracrine effects of WJ-MSC appear to improve wound healing, at least in mice [32].

2. Wound healing

As one of the largest organs of the human body, the skin has several vital roles, including a protective barrier against fluid loss, electrolyte imbalance, and microbial infections [33, 34]. Skin lesions are defined as any mechanical, thermal, or chemical damage to the skin that interferes with its function or fails to maintain its integrity [35, 36]. Wound healing is a complex, multi-step process that is often divided into three stages:

1. The inflammatory phase: In this phase, following the tissue injury, the process of hemostasis is initiated, and the resulting fibrin clots provide an extracellular matrix for the migration of the white blood cells (neutrophils and macrophages) and platelets. These elements play a pivotal role in wound healing. Although platelets affect wound healing by secreting various growth factors such as platelet-derived growth factor (PDGF), they are not essential for wound healing without bleeding. The next steps are the result of neutrophils' function against infections, foreign bodies, and pus. Then, the transformation of monocytes into macrophages indicates the end of this phase and the beginning of the proliferation stage [34, 37].

2. The proliferative phase: This phase is divided into several stages, including neoangiogenesis, fibroblast migration, epithelialization, granulation tissue formation and contraction [34, 37, 38]. In short, at this stage, the number of macrophages decreases, and granulation tissue begins to form. Migration of other cells, such as fibroblasts and keratinocytes, also begins. These cells secrete various growth factors and help the growth of granulation tissue. As more granulation tissue grows, more collagen is synthesized as a scaffold. The combination of these interactions

Rezaee et al.
causes the wound margin to close and eventually the wound to close.

3. Extracellular matrix regeneration stage: In this stage, which is the longest stage, collagen is regenerated. All these stages overlap to some extent [18, 33, 34, 38, 39].

Rezaee et al.

Figure 1 shows phases of wound healing. Limits vary within faded intervals, mainly by wound size and healing conditions, but the image does not include major impairments that cause chronic wounds.

Table 1. Risk factors of delay in wound healing

| Systemic                  | Local                      | Miscellaneous                                      |
|---------------------------|----------------------------|----------------------------------------------------|
| Advanced age              | Microbial infections       | Excess inflammatory mediators                      |
| Obesity                   | Exudates                  | Some medications (eg. Chemotherapeutic drugs, Corticosteroids, NSAIDs) |
| Renal Diseases            | Ischemia and necrosis     |                                                    |
| Malnutrition/Poor nutrition | Hypoxia               | Inappropriate keratinocytes proliferation          |
| Trauma                    |                            |                                                    |
| Diabetes Mellitus         |                            |                                                    |
| Vasculitis                |                            |                                                    |
| Hypothermia               |                            |                                                    |

and include the items listed in Table 1 [34, 41-44]. There are also factors that can facilitate healing such as a more profuse blood flow[45] [45], vitamin C [46], and more [34, 43, 47]. Unfortunately, chronic wounds remain a challenge because there is no sign of complete healing of these wounds [38]. Current treatments include both modern and traditional dressings [42, 48]. One interesting approach has been the use of hydrogel dressings and the conditioned media (stem cell secretome) of stem cells which showed promising results in both reducing scar
formation, and the healing rate in studies [41, 49, 50]. Some strategies to deal with chronic wounds challenge are antibiotics to prevent and treat infections, growth factors such as epidermal growth factors (EGF) or PDGF, or fibroblast growth factors. These factors affect the proliferative phase of wound healing [41, 51, 52]. Also, there are reports of immune-modulating molecules such as IL-4 in wound healing [41, 52, 53]. Despite all of these, stem cells offer a very bright horizon for future research and therapeutic applications [5, 6, 41, 51, 54-57]. Some studies have claimed that MSCs secrete vascular endothelial growth factor (VEGF), which can help regenerate the skin. These findings can potentially change the management of chronic wounds and our view of wound management in general [41, 58]. Stem cells are notable due to their vast potential in solving problems of current medicine, including wound healing [45, 59-62], diseases of the nervous system [63-67], diabetes mellitus [68, 69], Crohn’s disease [70], chronic myeloid leukemia [71, 72], heart failure [73, 74], liver cirrhosis [75, 76] and others.

3. Stem cells and their classification

Stem cells are undifferentiated cells with differing degrees of potential for differentiation, varying from unipotent (capable of differentiating into a single lineage) to totipotent (capable of differentiating into all cell types). These cells can "self-renew", which is defined as the generation of daughter cells utterly identical to the original cell. This ability can help preserve the limited pool of stem cells available at birth [77-83]. Stem cells are classified into two main categories based on the source of origin and potential for differentiation.

3.1 Classification of stem cells based on their origin

Embryonic: These cells are derived from the fetus’s internal cell mass and can form all three layers of the embryo [77]. Adult: These stem cells are derived from different adult cells with a differentiation capacity of at least one lineage. Recent studies show that some of them have can generate up to three lineages [81, 82, 84, 85].

3.2 Classification of stem cells based on the potential to differentiate

Unipotent: These are stem cells with the potential of differentiating into a single cell type that can produce a lineage, such as muscle stem cells that differentiate into adult muscle cells [77, 79, 86-89]. Oligopotent: These stem cells can generate two or more lineages but are limited to a specific tissue. A good example is the hematopoietic stem cells because these cells can differentiate into both myeloid and lymphoid lineages [90-92]. Multipotent: This type of stem cell is found in most tissues and can differentiate into cells from a single layer. MSCs are the most recognized in this class of stem cells. They can be taken from various tissues such as bone marrow, adipose tissue, Wharton's Jelly, umbilical cord, and peripheral blood [93-96], and differentiated into all mesoderm-derived tissues such as adipose, bone, cartilage, and muscle [96-99]. There have also been reports of "transdifferentiation", the differentiation of cells of one layer (MSCs) into the tissue of another layer (such as ectoderm-derived neuronal tissue) [90, 100]. Pluripotent: These cells have the potential to differentiate into cells from all three germ layers, ectoderm, endoderm, and mesoderm. Embryonic Stem Cells (ESCs) are examples of these stem cells that were first extracted from the inner cell mass of the blastocyst [90, 101]. Totipotent: Totipotent or omnipotent stem cells are the most undifferentiated cells and are only seen in early development. Fertilized oocytes and the daughter cells of the 1st and 2nd generation are examples of these cells that can differentiate into embryonic and extraembryonic tissues [90, 102].

4. Stem cells in wound healing

One issue to consider is that, despite all the evidence, long-term aspects of stem cell therapy and research are unknown, and its potentially harmful effects can be far more devastating than they seem. However, with more and long-term research, these concerns will be reduced [103, 104]. While the exact mechanisms of action of stem cells in wound healing have not yet been discovered, some aspects have been investigated. Various studies have shown that stem cells are involved in eliminating necrosis, neoangiogenesis, vascularization, reduction of scar formation, accelerated epithelialization and wound contraction [105-107]. These effects suggest that stem cell activity is beneficial for wound healing and reducing local inflammation. Most of these cases can
be attributed to signaling, which plays a crucial role in the stem cell effect during wound healing [32, 108, 109]. The studies have shown that transplanted mesenchymal stem cells release various growth factors and cytokines, which trigger the following two processes:

1. Promotes the migration and activity of fibroblasts and keratinocytes, which cause angiogenesis and healing of skin wounds and modulate the migration of leukocytes to the site of injury [110].

2. Release of immunosuppressive and anti-inflammatory agents, which reduce leukocyte proliferation and inflammation. Excessive inflammatory mediators are one of the predisposing factors for chronic skin wounds [47, 106]. Thus, mesenchymal stem cells enhance and improve the complex process of wound healing at all stages [111].

5. Mesenchymal stem cells (MSCs)

MSCs are adult stem cells that originate in the embryonic mesoderm layer. These stem cells are derived from a wide range of different tissues such as bone marrow, adipose tissue, nerve tissue, cord blood, and Wharton jelly [18, 32, 38, 77, 112-115]. These cells can self-renew, and despite years of research, a single specific marker has not yet been identified to identify and differentiate them. The best effort to achieve a uniform definition has been made by the Mesenchymal Stem Cell Committee and the International Cell Therapy Society, which defined mesenchymal stem cells as follows:

1. Plastic adhesive cells when stored in standard culture conditions.

2. Cells that should express (> 95%) CD105, CD73, and CD90 and lack the expression (<2%) of surface molecules CD45, CD34, CD14, or CD11b, CD79α or CD90, and HLA-DR.

3. Cells that should be differentiated into osteoblasts, adipocytes, and chondroblasts in vitro.

These are only a minimal set of standard criteria set up to facilitate data exchange amongst researchers and academia [116]. MSCs remain at the site of the skin wound, even after the wound has been closed. These cells play a pivotal role in almost all of the processes of inflammation, fibrosis, tissue repair, angiogenesis, wound contraction, scar development, and granulation tissue formation [117-120]. The studies have shown that mesenchymal stem cells have immunomodulatory effects such as inhibition of proliferation and reduced function in various immune cells, including natural killer (NK) cells, dendritic cells (DC), and lymphocytes [121-123]. Mesenchymal stem cells reduce the secretion of inflammatory cytokines [124] and secrete various anti-inflammatory cytokines such as TGFβ, IDO, PGE2, nitric oxide, IL-6, semaphorin-3A, and the Gal-1 and Gal-9 of galactins [125-131]. Some studies have used the MSCs conditioned mediums. These studies showed significant contributions to tissue regeneration and wound healing [5, 119, 132-135]. Interestingly, all mesenchymal stem cells appear to have some similarities, regardless of the tissue from which they are isolated. These similarities include nuclear cell markers, growth factors, and cytokines. In addition, there are differences, so when designing MSC-based treatments, differences such as their degree of differentiation and proliferation should be considered [136-138].

5.1 Bone marrow-derived stem cells (BMCs)

These stem cells are pluripotent and include mesenchymal stromal cells, hematopoietic stem cells, and even epithelial progenitor cells [139-141]. BMCs secrete various growth factors, cytokines, and exosomes [142, 143]. Many studies on different diseases such as myocardial infarctions (MI) [144, 145], chronic kidney disease (CKD) [146, 147], spinal cord injuries [140], and uveitis [148] have been undertaken. These stem cells have angiogenesis-inducing effects and a positive effect on microvasculature [139].

5.2 Adipose-derived stem cells (ASCs)

Stem cells derived from adipose tissue are yet another source of multipotent adult stem cells with numerous advantages compared to other sources of adult mesenchymal stem cells, given the massive pool of available adipose tissue and the minimally invasive extraction methods used [149]. Zuk et al. were the first to introduce this new source of mesenchymal stem cells around the turn of the century [150]. Some of the characteristics of these ASCs that have led to the interest taken in them are their anti-apoptotic, anti-inflammatory, proangiogenic, immunomodulatory, and anti-scarring effects [151]. Various studies have evaluated the therapeutic effects of ASCs on soft tissue regeneration, myocardial infarctions, ischemic...
5.3 Olfactory-Ecto mesenchymal stem cells (OE-MSCs)

These are a relatively novel population of stem cells present in the olfactory lamina propria [153]. As a population of stem cells, these cells boast a high proliferation rate, the potential to differentiate into multiple various lineages, self-renewal, as well as impressive immunomodulatory effects [154, 155]. One study found that the immunoregulation was mainly through T cell response [156].

5.4 Neural stem cells (NSCs)

NSCs are multipotent stem cells that have been the main target of interest in neural and spinal cord diseases [157, 158]. One major hurdle in their use, despite their beneficial secretions and differentiation into neurons, astrocytes, and oligodendrocytes, is the source from which they are derived, as well as the therapeutic approach that needs to be used be taken [159, 160].

5.5 Wharton’s jelly-mesenchymal stem cells

Wharton jelly-mesenchymal stem cells (WJ-MSCs) are mesenchymal stem cells isolated from the umbilical cord, especially connective tissue called Wharton’s jelly. What truly makes WJ-MSCs valuable is their immune-privileged status, high differentiation potential, easy isolation and collection, and minor moral issue. These stem cells have many features in common with embryonic stem cells, both phenotypically and genetically, although there are differences. Some common features are high ex vivo expansion capacity and a shorter cell cycle [161]. Wharton’s Jelly was first described in 1656 by Thomas Wharton as a mucosal connective tissue that separates the umbilical vessels and amniotic epithelium. Then in 1991, McElreavey et al. first isolated the WJ-MSC from the umbilical cord [162, 163]. Many studies have been performed using stem cells in various fields, including oncology, pulmonology, nephrology, neurology, and orthopedics [22-25, 164]. Due to the immunosuppressive and modulatory effect of mesenchymal stem cells, WJ-MSCs are very suitable candidates for use in allogeneic transplants for cell therapy. Some immunomodulatory properties of WJ-MSCs have been demonstrated in a study by Zhang et al. [165]. They observed that WJ-MSC grafting in burn wounds significantly showed wound healing and reduction of inflammatory markers. These results meant that the WJ-MSC transplant helped repair the skin by suppressing the secondary inflammatory response. There are reports of several methods of administering WJ-MSCs during stem cell therapy. These include local injections [165-167], topical administration [168-170], and systemic injections [171, 172]. Various methods have been used in studies in which topical administration has been investigated. In one study, Pourfath et al. sprayed WJ-MSC at the wound site [168], while in two other studies by Gholipour et al. [169, 170], mesenchymal stem cells were administered through seeding in tissue-engineered scaffolds. Although topical application of WJ-MSCs to skin wounds may seem to be the least invasive and available method of application of these cells, the merits of other prescriptions such as systemic injections are so high that they cannot be ignored. One of these competencies is that in local injection, over-cell dosing at the target site of skin ulcers is better controlled. On the other hand, the WJ-MSCs in the scaffold can help improve paracrine signaling and cell survival by keeping them out of the harsh environment after injection [173]. Problems with systemic use are primarily immune responses that do not concern the immune-privileged status of WJ-MSCs, and secondly, whether injected MSCs are present at the site of injury and participate in the healing process [173].

6. Therapeutic effects of WJ-MSCs in skin wound healing

Many studies have already been done on the clinical use of WJ-MSCs in wounds treatment. These studies [109, 174, 175] have been researching the healing properties of these stem cells on the rat, ovine, and sheep animal models. Due to ethical issues related to the unknown long-term effects of stem cells, most research regarding the use of WJ-MSCs in wound healing in animal studies. However, as of September 12, 2021, there are 50 clinical trials registered that are attempting to assess the effects of WJ-MSCs on a wide range of diseases, including erectile dysfunction, osteoarthritis, diabetes mellitus type 1, systemic sclerosis (scleroderma), myocardial infarctions, and no-option critical limb ischemia (NO-CLI). In addition to the aforementioned clinical trials listed, there are also two clinical trials, in which the use of Wharton's
jelly and umbilical cord are more directly assessed in the field of wound healing. The first one is Clinical trial NEOX® CORD 1K vs. Standard of Care in Non-healing Diabetic Foot Ulcers (CONDUCT I) (NCT02166294), which despite being completed, has yet to post any results. Furthermore, Hashemi et al. conducted a randomized clinical trial in which [176], they used an acellular amniotic membrane seeded with WJ-MSCs to cover the wounds. They concluded that the use of these stem cells with the scaffolding had significantly decreased the wound size, and wound healing time.

7. Clinical applications of WJ-derived stem cells in wounds treatment

Wharton jelly-derived MSCs have been widely studied as an unlimited, accessible, and promising source for skin wound healing. In 2014, Arno et al. showed that administration of human WJ-MSCs repaired skin wounds in a mouse model by increasing epithelialization, angiogenesis, as well as fibroblast proliferation and migration [32]. In a study, Zhang et al. examined the effect of subcutaneous injection of WJ-MSCs on an animal burn model. According to the results of this study, subcutaneous injection of WJ-MSCs suppresses secondary inflammation by reducing inflammatory cytokines and thus accelerates the skin repair process in burn models of mice [27]. Recently, the results of a study showed that because of the potential for epidermal differentiation and lack of HLA antigen expression, WJ-MSCs are more suitable sources for bioengineered human skin replacement compared to mesenchymal stem cells derived from other tissues such as bone marrow. They are fat and tooth pulp [177]. According to several studies on the mouse skin wound model, the use of WJ-MSCs could accelerate the formation of the epithelial layer, increase wound contraction, neovascularization and increase collagen production [178-180]. It has also been shown that the use of extracellular vesicles and medium conditioning derived from WJ-MSCs at the wound site enhances the proliferation and migration of fibroblasts to the site of injury, epithelialization, angiogenesis, regeneration of sebaceous glands and hair follicles [32, 181-183]. Application of WJ-MSCs combined with biocompatible scaffolds was also associated with reduced scar formation, wound healing time, and wound size [9, 176].

8. Concerns, dilemmas, ethical issues of the use of Wharton jelly stem cells in wound healing

Ethical issues with stem cells remain a challenge, although the use of cells such as the WJ-MSC can significantly reduce this. The primary concern is that stem cell therapies, besides the limited number of human studies, are ethical [184]. One major point against the use of these cells, especially embryonic stem cells, has always been that to supply enough stem cells, many embryos would have to be raised and killed. While some argue that considering the benefits of stem cell research and therapy, it can be justified in part, but public opinion is still not interested in serious action. On the other hand, in recent years, public opinion on the therapeutic uses of stem cells seems to have greatly improved. This improvement of public opinion is largely achieved through general education about the extraordinary untapped benefits and potential of stem cells in therapeutic fields [184, 185]. Furthermore, a specific study focusing on burn wounds showed that people fully accept stem cell therapy, especially autologous stem cells [186]. Fortunately, Clover et al. also showed that the general acceptance rate of allogeneic stem cells therapy is high and does not differ significantly for other diseases such as diabetes or Parkinson's [186]. Another concern that has diminished is immune system rejection and tumorigenesis that have been addressed in many articles [187-189]. In general, as research expands, our understanding of stem cells and the mechanism by which they affect living cells will improve, and more evidence will be discovered that stem cell therapy is safe [103, 104].

9. Conclusion and future perspectives

In summary, according to what was discussed in our study, the future of the use of stem cells, especially MSCs, in wound healing is auspicious. As science and technology advance, more innovative ways to meet the current challenges of stem cell therapy are being discovered. We believe that given the unique effects of WJ-MSCs on immunomodulation and its moral health, human studies and clinical trials should be conducted to provide further evidence of the safety and
efficacy of these cells as a cornerstone of the future of reconstructive medicine.

Acknowledgments
We would like to thank the Burn and Regenerative Medicine Research Center and its personnel for their assistance in the numerous steps of this research.

Authors’ contributions
All authors contributed equally in data collection and drafting of the manuscript. Also, all authors approved the final version of the manuscript.

Conflict of interests
The authors disclose no competing/conflicting interests.

Ethical declarations
Not applicable.

Financial support
No funding was received for this study.

References
1. Kim DJ, Mustoe T, Clark RA. Cutaneous wound healing in aging small mammals: a systematic review. Wound Repair Regen. 2015;23(3):318-39.
2. Agarwal PK, Singh A, Gaurav K, Goel S, Khanna HD, Goel RK. Evaluation of wound healing activity of extracts of plantain banana (Musa sapientum var. paradisiaca) in rats. Indian J Exp Biol. 2009;47(1):32-40.
3. Murthy S, Gautam MK, Goel S, Purohit V, Sharma H, Goel RK. Evaluation of in vivo wound healing activity of Bacopa monniera on different wound model in rats. Biomed Res Int. 2013;2013:972028.
4. Diegelmann RF, Evans MC. Wound healing: an overview of acute, fibrotic and delayed healing. Front Biosci. 2004;9:283-9.
5. Jayaraman P, Nathan P, Vasanthan P, Musa S, Govindasamy V. Stem cells conditioned medium: a new approach to skin wound healing management. Cell Biol Int. 2013;37(10):1122-8.
6. Ghieh F, Jurjus R, Ibrahim A, Geagea AG, Daouk H, El Baba B, et al. The Use of Stem Cells in Burn Wound Healing: A Review. Biomed Res Int. 2015;2015:684084.
7. Hassan WU, Greiser U, Wang W. Role of adipose-derived stem cells in wound healing. Wound Repair Regen. 2014;22(3):313-25.
8. Rajaimeakers MH. Overview of stem cells. 2019. Available from: https://www.uptodate.com/contents/overview-of-stem-cells
9. Sabapathy V, Sundaram B, V MS, Mankuzhy P, Kumar S. Human Wharton’s Jelly Mesenchymal Stem Cells plasticity augments scar-free skin wound healing with hair growth. PLoS One. 2014;9(4):e93726.
10. Abbaszadeh H, Ghorbani F, Derakhshani M, Movassaghpour AA, Yousefi M, Talebi M, et al. Regenerative potential of Wharton’s jelly-derived mesenchymal stem cells: A new horizon of stem cell therapy. J Cell Physiol. 2020;235(12):9230-40.
11. Cui HS, Joo SY, Cho YS, Park JH, Kim JB, Seo CH. Effect of Combining Low Temperature Plasma, Negative Pressure Wound Therapy, and Bone Marrow Mesenchymal Stem Cells on an Acute Skin Wound Healing Mouse Model. Int J Mol Sci. 2020;21(10):3675.
12. Peng Y, Xuan M, Zou J, Liu H, Zhuo Z, Wan Y, et al. Freeze-dried rat bone marrow mesenchymal stem cell paracrine factors: a simplified novel material for skin wound therapy. Tissue Eng Part A. 2015;21(5-6):1036-46.
13. Abo-Elkheir W, Hamza F, Elmofty AM, Emam A, Abd-Moktader M, Elsherefy S, et al. Role of cord blood and bone marrow mesenchymal stem cells in recent deep burn: a case-control prospective study. Am J Stem Cells. 2017;6(3):23-35.
14. Himal I, Goyal U, Ta M. Evaluating Wharton's Jelly-Derived Mesenchymal Stem Cells Survival, Migration, and Expression of Wound Repair Markers under Conditions of Ischemia-Like Stress. Stem Cells Int. 2017;2017:3295849.
15. Shii Y, Su J, Roberts AI, Shou P, Rabson AB, Ren G. How mesenchymal stem cells interact with tissue immune responses. Trends Immunol. 2012;33(3):136-43.
16. Tamaka M, Kerpedjeva SS. Acceleration of Wound Healing by Multiple Growth Factors and Cytokines Secreted from Multipotent Stromal Cells/Mesenchymal Stem Cells. Adv Wound Care (New Rochelle). 2012;1(4):177-82.
17. Doi H, Kitajima Y, Luo L, Yan C, Tertiary S, Ono Y, et al. Potency of umbilical cord blood- and Wharton's jelly-derived mesenchymal stem cells for scarless wound healing. Sci Rep. 2016;6:18844.
18. Kamolz LP, Keck M, Kasper C. Wharton's jelly mesenchymal stem cells promote wound healing and tissue regeneration. Stem Cell Res Ther. 2014;5(3):62.
19. Can A, Karahuseyinoglu S. Concise review: human umbilical cord stroma with regard to the source of fetus-derived stem cells. Stem Cells. 2007;25(11):2886-95.
20. Varaa N, Azandeh S, Khodabandeh Z, Gharavi AM. Wharton's Jelly Mesenchymal Stem Cell: Various Protocols for Isolation and Differentiation of Hepatocyte-Like Cells; Narrative Review. Iran J Med Sci. 2019;44(6):437-48.
21. Sobolewski K, Malkowski A, Bankowski E, Jaworski S. Wharton's jelly: a reservoir of peptide growth factors. Placenta. 2005;26(10):747-53.
22. Kuroda Y, Kitada M, Wakao S, Dezawa M. Mesenchymal stem cells and umbilical cord as sources for schwann cell differentiation: their potential in peripheral nerve repair. Open Tissue Eng Regen Med J. 2011;4(1):54-63.
23. Du T, Zou X, Cheng J, Wu S, Zhong L, Ju G, et al. Human Wharton's jelly-derived mesenchymal stromal cells reduce renal fibrosis through induction of native and foreign hepatocyte growth factor synthesis in injured tubular epithelial cells. Stem Cell Ther Regen Med. 2013;4(3):59.
24. Moodley Y, Atienza D, Manuepillai U, Samuel CS, Tchongue J, Ilancheran S, et al. Human umbilical cord mesenchymal stem cells reduce fibrosis of bleomycin-induced lung injury. Am J Pathol. 2009;175(1):303-13.
25. Lo Iacono M, Anzalone R, Corrao S, Giufrè M, Di Stefano A, Giannuzzi P, et al. Perinatal and wharton's jelly-derived mesenchymal stem cells in cartilage regenerative medicine and
tissue engineering strategies. Open Tissue Eng Regen Med J. 2011; 4(1):72-81.
26. Tamura M, Kawabata A, Ohta N, Uppalapati L, G Becker K, Troyer D. Wharton’s jelly stem cells as agents for cancer therapy. Open Tissue Eng Regen Med J. 2011; 4(1):39-47.
27. Zhang Y, Hao H, Liu J, Fu X, Han W. Repair and regeneration of skin injury by transplanting microparticles mixed with Wharton’s jelly and MSCs from the human umbilical cord. Int J Low Extrem Wounds. 2012; 11(4):264-70.
28. Tam K, Cheystryavandran S, Venugopal J, Biswas A, Choolani M, Ramakrishna S, et al. A nanoscaffold impregnated with human wharton’s jelly stem cells or its secretions improves healing of wounds. J Cell Biochem. 2014; 115(4):794-803.
29. Stefańska K, Ożegowska K, Hutchings G, Popis M, Moncrieff L, Domec C, et al. Human Wharton’s Jelly-Cellular Specificity, Stemness Potency, Animal Models, and Current Application in Human Clinical Trials. J Clin Med. 2020; 9(4):1102.
30. Prasanna SJ, Gopalakrishnan D, Shankar SR, Vasandan AB. Pro-inflammatory cytokines, IFNgamma and TNFalpha, influence immune properties of human bone marrow and Wharton jelly mesenchymal stem cells differentially. PLoS One. 2010; 5(2):e9016.
31. Deuse T, Stubendorff M, Tang-Quan K, Phillips N, Kay MA, Eiermann T, et al. Immunogenicity and immunomodulatory properties of umbilical cord lining mesenchymal stem cells. Cell Transplant. 2011; 20(5):655-67.
32. Arno AI, Amini-Nik S, Blit PH, Al-Shehab M, Belo C, Herer E, et al. Human Wharton’s jelly mesenchymal stem cells promote wound healing through paracrine signaling. Stem Cell Res Ther. 2014; 5(1):28.
33. Graham-Brown R, Burns T. Dermatology: lecture notes: John Wiley & Sons; 2011.
34. Singh AJ, Clark RA. Cutaneous wound healing. N Engl J Med. 1999; 341(10):738-46.
35. Kujath P, Michelsen A. Wounds - from physiology to wound dressing. Dtsch Arztebl Int. 2008; 105(13):239-48.
36. Mobayen M, Rimaz S, Malekshahi A. Evaluation of clinical and laboratory causes of burns in pre-school children. J Curr Biomed Rep. 2021; 21(1):27-31.
37. Spear M. Acute or chronic? What’s the difference? Plast Surg Nurs. 2013; 33(2):98-100.
38. García Guillen A, Millán Rivero J, Martínez C, Moraleda J, García-Bernal D. Wharton’s Jelly Mesenchymal Stem Cell Therapy for Skin Wound Healing. J Stem Cell Res Dev. 2020; 6:039.
39. Coutinho P, Qiu C, Frank S, Tamber K, Becker D. Dynamic changes in connexin expression correlate with key events in the wound healing process. Cell Biol Int. 2003; 27(7):525-41.
40. Haggstrom M. Medical gallery of mikel haggstrom 2014. Wiki J Med. 2014; 1(2):1-53.
41. Lopes B, Sousa P, Alvites R, Branquinho M, Sousa A, Mendonça C, et al. The Application of Mesenchymal Stem Cells on Wound Repair and Regeneration. Appl Sci. 2021; 11(7):3000.
42. Rezvani Ghomi E, Khalili S, Nouri Khorasani S, Esmaeely Neisiany R, Ramakrishna S. Wound dressings: Current advances and future directions. J Appl Polym Sci. 2019; 136(27):47738.
43. Ojeh N, Pastar I, Tomic-Canic M, Stojadinovic O. Stem Cells in Skin Regeneration, Wound Healing, and Their Clinical Applications. Int J Mol Sci. 2015; 16(10):25476-501.
44. Xiong S, Zhang X, Lu P, Wu Y, Wang Q. A Gelatin-sulfonated Silk Composite Scaffold based on 3D Printing Technology Enhances Skin Regeneration by Stimulating Epidermal Growth and Dermal Neovascularization. Sci Rep. 2017; 7(1):4288.
45. Dash NR, Dash SN, Routray P, Mohapatra S, Mohapatra PC. Targeting nonhealing ulcers of lower extremity in human through autologous bone marrow-derived mesenchymal stem cells. Rejuvenation Res. 2009; 12(5):359-66.
46. Ohanube G, Obeta UM, Ikeagwulonu CR. Case reports in the use of vitamin C based regimen in prophylaxis and management of COVID-19 among Nigerians. J Curr Biomed Rep. 2020; 1(2):77-80.
47. Grada A, Falanga V. Novel Stem Cell Therapies for Applications to Wound Healing and Tissue Repair. Surg Technol Int. 2016; 29:29-37.
48. Dorai AA. Wound care with traditional, complementary and alternative medicine. Indian J Plast Surg. 2012; 45(2):418-24.
49. Zhang C, Wang T, Zhang L, Chen P, Tang S, Chen A, et al. Combination of lyophilized adipose-derived stem cell concentrated conditioned medium and polysaccharide hydrogel in the inhibition of hypertrophic scarring. Stem Cell Res Ther. 2021; 12(1):23.
50. Li M, Zhong L, He W, Ding Z, Hou Q, Zhao Y, et al. Concentrated Conditioned Medium-Loaded Silk Nanofiber Hydrogels with Sustained Release of Bioactive Factors To Improve Skin Regeneration. ACS Appl Bio Mater. 2019; 2(10):4397-407.
51. Das S, Baker AB. Biomaterials and Nanotherapeutics for Enhancing Skin Wound Healing. Front Biotechnol. 2016; 4:82.
52. Chouhan D, Dey N, Bhardwaj N, Mandal BB. Emerging and innovative approaches for wound healing and skin regeneration: Current status and advances. Biomaterials. 2019; 216:119267.
53. Cable J, Fuchs E, Weissman I, Jasper H, Glass D, Rando TA, et al. Adult stem cells and regenerative medicine—a symposium report. Ann N Y Acad Sci. 2020; 1462(1):27-36.
54. Devreecly LR, Boxer L, Myers MJ, Skasko M, Screven R. Questions and Challenges in the Development of Mesenchymal Stromal/Stem Cell-Based Therapies in Veterinary Medicine. Tissue Eng Part B Rev. 2017; 23(5):462-70.
55. Kanji S, Das H. Advances of Stem Cell Therapeutics in Cutaneous Wound Healing and Regeneration. Mediators Inflamm. 2017; 2017:5217967.
56. Nakamura Y, Ishikawa H, Kawai K, Tabata Y, Suzuki S. Enhanced wound healing by topical administration of mesenchymal stem cells transfected with stromal cell-derived factor-1. Biomaterials. 2013; 34(37):9393-400.
57. Hu M, Ludlow D, Alexander JS, McLarty J, Lian T. Improved wound healing of postischemic cutaneous flaps with the use of bone marrow-derived stem cells. Laryngoscope. 2014; 124(3):642-8.
58. Xiao Y, Peng J, Liu Q, Chen L, Shi K, Han R, et al. Ultrasmall CuS@BSA nanoparticles with mild photothermal conversion synergistically induce MSCs-differentiated fibroblast and improve skin regeneration. Theranostics. 2020; 10(4):1500-13.
59. Isakson M, de Blacam C, Whelan D, McArdle A, Clover AJ. Evidence and Future Potential. Stem Cell Therapies in Veterinary Medicine. 2016; 1462(1):27-36.
61. Valiente MR, Nicolás FJ, García-Hernández AM, Fuente Mora C, Blanquer M, Alcaraz PJ, et al. Cryopreserved amniotic membrane in the treatment of diabetic foot ulcers: a case series. J Wound Care. 2018; 27(12):806-15.

62. Liu D, Chen B, Liang Z, Deng W, Jiang Y, Li S, et al. Comparison of bone marrow mesenchymal stem cells with bone marrow-derived mononuclear cells for treatment of diabetic critical limb ischemia and foot ulcer: a double-blind, randomized, controlled trial. Diabetes Res Clin Pract. 2011; 92(1):26-36.

63. Rabinovich SS, Seledtsov VI, Banul NV, Poveshchenko OV, Senyukov VV, Astrakov SV, et al. Cell therapy of brain stroke. Bull Exp Biol Med. 2005; 139(1):126-8.

64. Resnick IB, Metodiev K, Lazarova P. Hematopoietic cell transplantation for autoimmune diseases: a review of history, current state, and future issues. Immunotherapy-Myths, Reality, Ideas, Future. 2017.

65. Lindvall O, Kokaia Z. Stem cells for the treatment of neurological disorders. Nature. 2006; 441(7097):1094-6.

66. Mackay-Sim A, Feron F, Cochrane J, Bassingthwaighte L, Bayliss C, Davies W, et al. Autologous olfactory ensheathing cell transplantation in human paraplegia: a 3-year clinical trial. Brain. 2008; 131(Pt 9):2376-86.

67. Yang FC, Riordan SM, Winter M, Gan L, Smith PG, Vivian JL, et al. Fate of Neural Progenitor Cells Transplanted Into Jaundiced and Nonjaundiced Rat Brains. Cell Transplant. 2017; 26(4):605-11.

68. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol. 2008; 26(4):443-52.

69. Trivedi HI, Vanikar AV, Thakker U, Firoze A, Dave SD, Patel Y. Human adipose tissue-derived mesenchymal stem cells combined with hematopoietic stem cell transplantation synthesize insulin. Transplant Proc. 2008; 40(4):1135-9.

70. Mishra R, Dhawan P, Srivastava AS, Singh AB. Inflammatory bowel disease: Therapeutic limitations and prospective of the stem cell therapy. World J Stem Cells. 2020; 12(10):1050-66.

71. Gratzwohl A, Heim D. Current role of stem cell transplantation in chronic myeloid leukaemia. Best Pract Res Clin Haematol. 2009; 22(3):431-43.

72. Hackanson B, Waller CF. Long-term follow-up of patients with chronic myeloid leukemia having received autologous stem cell transplantation. Ann Hematol. 2011; 90(4):395-9.

73. Menasché P, Alferi O, Janssens S, McKenna W, Reichenspurmer H, Trinquart L, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation. 2008; 117(9):1189-200.

74. Hagège AA, Marolleau JP, Vilquin JT, Alhérithère A, Peyrard S, Duboc D, et al. Skeletal myoblast transplantation in ischemic heart failure: long-term follow-up of the first phase I cohort of patients. Circulation. 2006; 114(1 Suppl):I108-13.

75. Kuo TK, Hung SP, Chuang CH, Chen CT, Shih YR, Fang SC, et al. Stem cell therapy for liver disease: parameters governing the success of using bone marrow mesenchymal stem cells. Gastroenterology. 2008; 134(7):2111-21, 21.e1-3.

76. Pai M, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, et al. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. Am J Gastroenterol. 2008; 103(8):1952-8.

77. Rostamzadeh A, Anjomshoaa M, Kurd S, Chai J-K, Jahangiri F, Niforouzhshad MA, et al. The role of Wharton's jelly mesenchymal stem cells in skin reconstruction. J Skin Stem Cell. 2015; 2(2):e60143.

78. Sundelacruz S, Kaplan DL. Stem cell- and scaffold-based tissue engineering approaches to osteochondral regenerative medicine. Semin Cell Dev Biol. 2009; 20(6):646-55.

79. Simon C, Pellier A. Stem cells in human reproduction: basic science and therapeutic potential: CRC Press; 2009.

80. Bongo A, Fong C-Y. Human Embryonic Stem Cells: Their Nature, Properties, and Uses. In: Baharvand H, editor. Trends in Stem Cell Biology and Technology. Totowa, NJ: Humana Press; 2009, p. 1-17.

81. Alison MR, Poulsom R, Forbes S, Wright NA. An introduction to stem cells. J Pathol. 2002; 197(4):419-23.

82. Li L, Xie T. Stem cell niche: structure and function. Annu Rev Cell Dev Biol. 2005; 21:605-31.

83. Smith A. The battlefield of pluripotency. Cell. 2005; 123(5):757-60.

84. Fu RH, Wang YC, Liu SP, Huang CM, Kang YH, Tsai CH, et al. Differentiation of stem cells: strategies for modifying surface biomaterials. Cell Transplant. 2011; 20(1):37-47.

85. Nandedkar T, Narkar M. Stem cell research: its relevance to reproductive biology. Indian J Exp Biol. 2003; 41(7):724-39.

86. Beck B, Blanpain C. Mechanisms regulating epidermal stem cells. Embo J. 2012; 31(9):2067-75.

87. Overturf K, al-Dhalimi M, Ou CN, Finegold M, Grompe M. Serial transplantation reveals the stem-cell-like regenerative potential of adult mouse hepatocytes. Am J Pathol. 1997; 151(5):1273-80.

88. de Rooij DG, Grootegeest JA. Spermatogonial stem cells. Curr Opin Cell Biol. 1998; 10(6):694-701.

89. Bentzinger CF, Wang YX, von Maltzahn J, Rudnicki MA. The emerging biology of muscle stem cells: strategies for modifying surface biomaterials. Bioessays. 2013; 35(3):231-41.

90. Kolios G, Moodley Y. Introduction to stem cells and regenerative medicine. Respiration. 2013; 85(3):3-10.

91. Majo F, Rochat A, Nicolas M, Jaouédé G, Barrandon Y. Oligopotent stem cells are distributed throughout the mammalian ocular surface. Nature. 2008; 456(7219):250-4.

92. Marone M, De Ritis D, Bonanno G, Mozzetti S, Rutella S, Scambia G, et al. Cell cycle regulation in human hematopoietic stem cells: from biology to clinical use. Exp Biol Med. 2005; 230(4):550-62.

93. Kramer M, Franchini M, Pizzolo G, Aprilli G. Mesenchymal stem cells: from biology to clinical use. Blood Transfus. 2007; 5(3):120-9.

94. Jaenisch R, Young R. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell. 2008; 132(4):567-82.

95. Ratajczak MZ, Zuba-Surma E, Kucia M, Poniewierska A, Suszyńska M, Ratajczak J. Pluripotent and multipotent stem cells in adult tissues. Adv Med Sci. 2012; 57(1):1-17.

96. Angello A, Kurth TB, De Bari C. Mesenchymal stem cells: a perspective from in vitro cultures to in vivo migration and niches. Eur Cell Mater. 2010; 20:121-33.
97. Bruder SP, Jaiswal N, Haynesworth SE. Growth kinetics, self-renewal, and the osteogenic potential of purified human mesenchymal stem cells during extensive subcultivation and following cryopreservation. J Cell Biochem. 1997; 64(2):278-94.
98. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science. 1997; 276(5309):71-4.
99. Friedenstein AJ, Challakhkan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet. 1970; 3(4):393-403.
100. Barzilay R, Melamed E, Offen D. Introducing transcription factors to multipotent mesenchymal stem cells: making transdifferentiation possible. Stem Cells. 2009; 27(10):2509-15.
101. Evans MJ, Kaufman MH. Establishment in culture of pluripotent stem cells. Science. 1981; 21(8):1201
102. Rossant J. Stem cells from the Mammalian blastocyst. Stem Cells. 2001; 19(6):477-82.
103. Gauthaman K, Fong CY, Suganya CA, Subramanian A, Biswas A, Choolani M, et al. Extra-embryonic human Wharton’s jelly stem cells do not induce tumorgenesis, unlike human embryonic stem cells. Reprod Biomed Online. 2012; 24(2):235-46.
104. Takagi R, Ishimaru J, Sugawara A, Toyoshima KE, Ishida K, Ogawa M, et al. Bioengineering a 3D integumentary organ system from iPS cells using an in vivo transplantation model. Sci Adv. 2016; 2(4):e1500887.
105. Cerqueira MT, Marques AP, Reis RL. Using stem cells in skin regeneration: possibilities and reality. Stem Cells Dev. 2012; 21(8):1201-14.
106. Rezaie F, Momeni-Moghaddam M, Naderi-Meshkin H. Regeneration and Repair of Skin Wounds: Various Strategies for Treatment. Int J Low Extrem Wounds. 2019; 18(3):247-61.
107. Ochiai H, Kishi K, Kubota Y, Oka A, Hirata E, Yabuki H, et al. Transplanted mesenchymal stem cells are effective for skin regeneration in acute cutaneous wounds of pigs. Regen Ther. 2017; 7:8-16.
108. Li JY, Ren KK, Zhang WJ, Xiao L, Wu HY, Liu QY, et al. Human amniotic mesenchymal stem cells and their paracrine factors promote wound healing by inhibiting heat stress-induced skin cell apoptosis and enhancing their proliferation through activating PI3K/AKT signaling pathway. Stem Cell Res Ther. 2019; 10(1):247.
109. Cerqueira MT, Pirrao RC, Marques AP. Stem Cells in Skin Wound Healing: Are We There Yet? Adv Wound Care (New Rochelle). 2016; 5(4):164-75.
110. He P, Zhao J, Zhang J, Li B, Gou Z, Gou M, et al. Bioprinting of skin constructs for wound healing. Burns Trauma. 2018; 6:5.
111. Hu MS, Borrelli MR, Lorenz HP, Longaker MT, Wan DC. Mesenchymal Stromal Cells and Cutaneous Wound Healing: A Comprehensive Review of the Background, Role, and Therapeutic Potential. 2018; 2018:6961983.
112. Hassouna A, Elgwaal M, Falmy H. Stromal stem cells: nature, biology and potential therapeutic applications. Stromal Cells-Structure, Function, and Therapeutic Implications. 2019.
113. Huang YZ, Xie HQ, Silini A, Parolini O, Zhang Y, Deng L, et al. Mesenchymal Stem/Progenitor Cells Derived from Articular Cartilage, Synovial Membrane and Synovial Fluid for Cartilage Regeneration: Current Status and Future Perspectives. Stem Cell Rev. 2017; 13(5):575-86.
mesenchymal stem cells associated with indoleamine 2,3-dioxygenase expression. Transplantation. 2010; 90(12):1312-20.

130. Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells. 2006; 24(2):386-98.

131. English K. Mechanisms of mesenchymal stromal cell immunomodulation. Immunol Cell Biol. 2013; 91(1):19-26.

132. Walter MN, Wright KT, Fuller HR, MacNeil S, Johnson WE. Mesenchymal stromal cell-conditioned medium accelerates skin wound healing: an in vitro study of fibroblast and keratinocyte scratch assays. Exp Cell Res. 2010; 316(7):1271-81.

133. Chen L, Xu Y, Zhao J, Zhang Z, Yang R, Xie J, et al. Conditioned medium from hypoxic bone marrow-derived mesenchymal stem cells enhances wound healing in mice. PLoS One. 2014; 9(4):e96161.

134. Kim JY, Song SH, Kim KL, Ko JJ, Im JE, Yie SW, et al. Human cord blood-derived endothelial progenitor cells and their conditioned media exhibit therapeutic equivalence for diabetic wound healing. Cell Transplant. 2010; 19(12):1635-44.

135. Santos JM, Camões SP, Filipe E, Cipriano M, Barcia RN, Filipe M, et al. Three-dimensional spheroid cell culture of umbilical cord tissue-derived mesenchymal stromal cells leads to enhanced paracrine induction of wound healing. Stem Cell Res Ther. 2015; 6(1):90.

136. Li CY, Wu XY, Tong JB, Yang XX, Zhao JL, Zheng QF, et al. Conditioned medium from hypoxic bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006; 24(5):1294-301.

137. Heo JS, Choi Y, Kim HS, Kim HO. Comparison of molecular profiles of human mesenchymal stem cells derived from bone marrow, umbilical cord blood, placenta and adipose tissue. Int J Mol Med. 2016; 37(1):115-25.

138. Kern S, Eichler H, Stoeve J, Klüter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006; 24(5):1294-301.

139. Golle L, Gerth HU, Beul K, Heitplatz B, Barth P, Fobker M, et al. Bone marrow-derived cells and their conditioned medium induce microvascular repair in uremic rats by stimulation of endogenous repair mechanisms. Sci Rep. 2017; 7(1):9444.

140. Cantinieux D, Quertainmont R, Blacher S, Rossi L, Wanet T, Noël A, et al. Conditioned medium from bone marrow-derived mesenchymal stromal cells improves recovery after spinal cord injury in rats: an original strategy to avoid cell transplantation. PLoS One. 2013; 8(8):e69515.

141. Kassem M, Abdallah BM. Human bone-marrow-derived mesenchymal stem cells: biological characteristics and potential role in therapy of degenerative diseases. Cell Tissue Res. 2008; 331(1):157-63.

142. Shi C. Recent progress toward understanding the physiologic function of bone marrow mesenchymal stem cells. Immunology. 2012; 136(2):133-8.

143. Ratafiaiczak J, Kucia M, Mierzewska K, Marlicz W, Pietrzkowski Z, Wojakowski W, et al. Paracrine proangiopoietic effects of human umbilical cord blood-derived purified CD133+ cells—implications for stem cell therapies in regenerative medicine. Stem Cells Dev. 2013; 22(3):422-30.

144. Assmus B, Leistner DM, Schächinger V, Erbs S, Elsässer A, Haberbosch W, et al. Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: migratory capacity of administered cells determines event-free survival. Eur Heart J. 2014; 35(19):1275-83.

145. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, HölscherHmann H, et al. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J. 2006; 27(23):2775-83.

146. Yuen DA, Connelly KA, Advani A, Liao C, Kuliszewski MA, Trogadis J, et al. Culture-modified bone marrow cells attenuate cardiac and renal injury in a chronic kidney disease rat model via an antifibrotic mechanism. PLoS One. 2010; 5(3):e9543.

147. van Koppen A, Joles JA, van Balkom BW, Lim SK, de Klein D, Giles RH, et al. Human embryonic mesenchymal stem cell-derived conditioned medium rescues kidney function in rats with established chronic kidney disease. PLoS One. 2012; 7(6):e38746.

148. Bermudez MA, Sendon-Lago J, Seoane S, Eiro N, Gonzalez F, Saa J, et al. Anti-inflammatory effect of conditioned medium from human uterine cervical stem cells in uveitis. Exp Eye Res. 2016; 149:84-92.

149. Frese L, Dijkman PE, Hoerstrup SP. Adipose Tissue-Derived Stem Cells in Regenerative Medicine. Transfus Med Hemother. 2016; 43(4):268-74.

150. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JJ, Mizuno H, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002; 13(12):4279-95.

151. Bertolini F, Lohsirawat V, Petit JY, Kolonin MG. Adipose tissue cells, lipotransfer and cancer: a challenge for scientists, oncologists and surgeons. Biochim Biophys Acta. 2012; 1826(1):209-14.

152. Cecarelli S, Pontecorvi P, Anastasiadou E, Napoli C, Marchese C. Immunomodulatory Effect of Adipose-Derived Stem Cells: The Cutting Edge of Clinical Application. Front Cell Dev Biol. 2020; 8:236.

153. Tian J, Zhu Q, Zhang Y, Bian Q, Hong Y, Shen Z, et al. Olfactory Ecto-Mesenchymal Stem Cell-Derived Exosomes Ameliorate Experimental Colitis via Modulating Th1/Th17 and Treg Cell Responses. Front Immunol. 2020; 11:598322.

154. Nivet E, Vignes M, Girard SD, Pierrisnard C, Baril N, Devèze A, et al. Engraftment of human nasal olfactory stem cells restores neuroplasticity in mice with hippocampal lesions. J Clin Invest. 2011; 121(7):2808-20.

155. Delorme B, Nivet E, Gaillard J, Häupl T, Ringe J, Devèze A, et al. The human nose harbors a niche of olfactory ectomesenchymal stem cells displaying neurogenic and osteogenic properties. Stem Cells Dev. 2010; 19(6):853-66.

156. Rui K, Zhang Z, Tian J, Lin X, Wang X, Ma J, et al. Olfactory ecto-mesenchymal stem cells possess immunoregulatory function and suppress autoimmune arthritis. Cell Mol Immunol. 2016; 13(3):401-8.

157. Ourendik J, Ourendik V, Lynch WP, Schachner M, Snyder EY. Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. Nat Biotechnol. 2002; 20(11):1103-10.

158. Okano H. Stem cell biology of the central nervous system. J Neurosci Res. 2002; 69(6):698-707.

159. Tang Y, Yu P, Cheng L. Current progress in the derivation and therapeutic application of neural stem cells. Brain Res. 2018; 1610:3108.

160. Rong Y, Liu W, Wang J, Fan J, Luo Y, Li L, et al. Neural stem cell-derived small extracellular vesicles attenuate apoptosis and...
neuroinflammation after traumatic spinal cord injury by activating autophagy. Cell Death Dis. 2019; 10(3):340.

161. Marino L, Castakl MA, Rosamilio R, Ragni E, Vitolo R, Fulgione C, et al. Mesenchymal Stem Cells from the Wharton’s Jelly of the Human Umbilical Cord: Biological Properties and Therapeutic Potential. Int J Stem Cells. 2010; 12(2):218-26.

162. McLearney KD, Irvine AI, Ennis KT, McLean WH. Isolation, culture and characterisation of fibroblast-like cells derived from the Wharton’s jelly portion of human umbilical cord. Biochem Soc Trans. 1991; 19(1):298.

163. Lindahl A. 5,514 - Chondrocyte Transplantation and Selection. In: Ducheyne P, editor. Comprehensive Biomaterials. Oxford: Elsevier; 2011. p. 189-98.

164. EM S. Cell therapy for the treatment of metabolic liver disease: an update on the umbilical cord derived stem cells candidates. Open Tissue Eng Regen Med J. 2011; 4(1):48-53.

165. Zhang J, Li X, Fan L, Li P, Yu Y, Huang Y, et al. Immunosuppressive effects of mesenchymal stem cell transplantation in rat burn models. Int J Clin Exp Pathol. 2015; 8(5):5199-36.

166. Zhang B, Wang M, Gong A, Zhang X, Wu X, Zhu Y, et al. HucMSC-Exosome Mediated-Wnt4 Signaling Is Required for Cutaneous Wound Healing. Stem Cells. 2015; 33(7):2158-68.

167. Shi H, Xu X, Zhang B, Xu J, Pan Z, Gong A, et al. 3,3’-Dindolylmethane stimulates exosomal Wnt11 autocrine signaling in human umbilical cord mesenchymal stem cells to enhance wound healing. Theranostics. 2017; 7(6):1674-88.

168. Pourfath MR, Behzad-Behbahani A, Hashemi SS, Derakshanfar A, Taheri MN, Salehi S. Monitoring wound healing of burn in rat model using human Wharton’s jelly mesenchymal stem cells containing cGFP integrated by lentiviral vectors. Iran J Basic Med Sci. 2018; 21(1):70-6.

169. Gholipour-Kanani A, Bahrami SH, Joghataie MT, Samadikuchaksaraei A, Ahmadi-Tafti H, Rabhani S, et al. Tissue engineered poly(caprolactone)-chitosan-poly(vinyl alcohol) nanofibrous scaffolds for burn and cutting wound healing. IET Nanobiotechnol. 2014; 8(2):123-31.

170. Gholipour-Kanani A, Bahrami SH, Samadi-Koachansarae A, Ahmadi-Tafti H, Rabhani S, Kororian A, et al. Effect of tissue-engineered chitosan-poly(vinyl alcohol) nanofibrous scaffolds on healing of burn wounds of rat skin. IET Nanobiotechnol. 2012; 6(4):129-35.

171. Liu L, Yu Y, Hou Y, Chai J, Duan H, Chu W, et al. Human umbilical cord mesenchymal stem cells transplantation promotes cutaneous wound healing of severe burned rats. PLoS One. 2014; 9(2):e88348.

172. Liu L, Song H, Duan H, Chai J, Yang J, Li X, et al. TSG-6 secreted by human umbilical cord-MSCs attenuates severe burn-induced excessive inflammation via inhibiting activations of P38 and JNK signaling. Sci Rep. 2016; 6:30121.

173. Rangatchew F, Vester-Glowinski P, Rasmussen BS, Hastrup E, Munthe-Fog L, Talman ML, et al. Mesenchymal stem cell therapy of acute thermal burns: A systematic review of the effect on inflammation and wound healing. Burns. 2021; 47(2):270-94.

174. Takeo M, Lee W, Ito M. Wound healing and skin regeneration. Cold Spring Harb Perspect Med. 2015; 5(1):a023267.

175. Campos JM, Sousa AC, Caseiro AR, Pedrosa SS, Pinto PO, Branquinho MV, et al. Dental pulp stem cells and Bonelike® for bone regeneration in ovine model. Regen Biomater. 2019; 6(1):49-59.

176. Hashemi SS, Mohammad M, Amin M, et al. The healing effect of Wharton’s jelly stem cells seeded on biological scaffold in chronic skin ulcers: A randomized clinical trial. J Cosmet Dermatol. 2010; 18(6):1961-7.

177. Martin-Piedra MA, Alfonso-Rodriguez CA, Zapater A, Durand-Herrera D, Chato-Astrain J, Campos F, et al. Effective use of mesenchymal stem cells in human skin substitutes generated by tissue engineering. Eur Cell Mater. 2019; 37:233-49.

178. Millán-Rivero JE, Martínez CM, Romecín PA, Aznar-Cervantes SD, Carpes-Ruiz M, Cenis JL, et al. Silk fibroin scaffolds seeded with Wharton’s jelly mesenchymal stem cells enhance epithelialization and reduce formation of scar tissue after cutaneous wound healing. Stem Cell Res Ther. 2019; 10(1):126.

179. Somal A, Bhat IA, Singal AP, Panda BSK, Desingu PA, et al. Impact of Cryopreservation on Caprine Fetal Adnexa Derived Stem Cells and Its Evaluation for Growth Kinetics, Phenotypic Characterization, and Wound Healing Potential in Xenogenic Rat Model. J Cell Physiol. 2017; 232(8):2186-200.

180. Shohara R, Yamamoto A, Takikawa S, Iwase A, Hibi H, Kikkawa F, et al. Mesenchymal stromal cells of human umbilical cord Wharton’s jelly accelerate wound healing by paracrine mechanisms. Cytotherapy. 2012; 14(10):1171-81.

181. Sun J, Zhang Y, Song X, Zhu J, Zhu Q. The Healing Effects of Conditioned Medium Derived from Mesenchymal Stem Cells on Radiation-Induced Skin Wounds in Rats. Cell Transplant. 2019; 28(1):105-15.

182. Fong CY, Tam K, Cheyyatraividran S, Gan SU, Gauthaman K, Armugam A, et al. Human Wharton’s jelly stem cells and its conditioned medium enhance healing of excisional and diabetic wounds. J Cell Biochem. 2014; 115(2):290-302.

183. Zhao G, Liu F, Liu Z, Zuo K, Wang B, Zhang Y, et al. MSC-derived exosomes attenuate cell death through suppressing AIF nucleus translocation and enhance cutaneous wound healing. Stem Cell Res Ther. 2020; 11(1):174.

184. Sandel MJ. Embryo ethics—the moral logic of stem-cell research. N Engl J Med. 2004; 351(3):207-9.

185. Einsiedel E, Premji S, Geransar R, Orton NC, Thavaratnam T, Bennett LK. Diversity in public views toward stem cell sources and policies. Stem Cell Rev Rep. 2009; 5(2):102-7.

186. Clover AJ, O’Neill BL, Kumar AH. Analysis of attitudes toward the source of progenitor cells in tissue-engineered products for use in burns compared with other disease states. Wound Repair Regen. 2012; 20(3):311-6.

187. Leal EC, Carvalho E, Tellechea A, Kafanas A, Tecilazich F, Kearney C, et al. Substance P promotes wound healing in diabetes by modulating inflammation and macrophage phenotype. Am J Pathol. 2015; 185(6):1638-48.

188. Duscher D, Barrera J, Wong VW, Maan ZN, Whittam AJ, Januszyn M, et al. Stem Cells in Wound Healing: The Future of Regenerative Medicine? A Mini-Review. Gerontology. 2016; 62(2):216-25.

189. Strong AL, Neumeister MW, Levi B. Stem Cells and Tissue Engineering: Regeneration of the Skin and Its Contents. Clin Plast Surg. 2017; 44(3):635-50.