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Mini Review

Exosomes and Stem Cell Therapy Advancements Accelerated and Improved Burn Wound Healing

Maisa Ribeiro*

Department of Medicine, Mineiros University Center, Mineiros, Brazil

ABSTRACT

Burn injuries pose a significant public health challenge, particularly in conflict-affected regions, leading to debilitating functional and cosmetic impairments. Current treatment options include debridement, skin grafts, and silicone therapy, but they have limitations in addressing the complex nature of burn wounds. Stem cell therapy, especially using Mesenchymal Stem Cells (MSCs), offers a potential avenue for enhancing natural skin regeneration processes. MSC-based therapy has demonstrated efficacy in promoting wound healing by modulating inflammation, promoting angiogenesis, and facilitating tissue regeneration. Various stem cell sources, such as Adipose-Derived Stem Cells (ADSCs), Bone Marrow-Derived MSCs (BM-MSCs), and umbilical cord blood MSCs, have been explored for their therapeutic potential in burn wound management. Despite the potential outcomes, challenges such as protocol standardization, long-term follow-up, and patient selection optimization persist. Nonetheless, stem cell therapy holds significant potential for revolutionizing burn injury treatment and improving patient outcomes. Further research is needed to elucidate the underlying mechanisms and optimize treatment strategies for effective translation into clinical practice.

Keywords: Stem cells; Burn would healing; Exosomes

INTRODUCTION

Burn injuries are significant would due to their prevalence and sequelae, particularly in regions affected by armed conflicts. These injuries can have debilitating functional and cosmetic consequences, highlighting the urgent need for enhanced and more efficient treatments [1,2]. There are three main classifications of burn wounds: Full-thickness burns, which deeply penetrate the skin layers and reach the underlying muscle; partial-thickness burns, which damage the skin layers without affecting the muscle; and superficial burns, which only irritate the skin surface [2,3]. Burn injuries compromise the body's overall integrity and impede skin regeneration. Current treatment modalities include debridement and skin grafts to aid in the healing process. Following the healing process, attention shifts to managing scars and their associated complications [4]. Burn scar care is focused on preserving the function of affected limbs and improving their cosmetic appearance. Initiation of treatment shortly after wound re-epithelialization is important, as it is most effective during the early, dynamic phase of healing and less so for older scars. Silicone therapy has emerged as a key approach for both preventing and treating keloids and hypertrophic scars. Although, silicone therapy is not without drawbacks, including potential for hypertrophic scarring, adherence issues, and contracture development [5].

An effective approach to overcome these challenges involves enhancing the natural skin regeneration process through the integration of stem cells into surgical procedures, a method currently being employed with the aim of reducing mortality risks [4,6]. Stem cells have demonstrated the ability to facilitate the healing of various types of wounds. Researchers worldwide are exploring the potential applications of stem cells sourced from diverse tissues and organs of the body. These sources include cord blood endothelial cells, amniotic cells, adipose-derived stem cells, circulating T cells and bone morrow [7-9].

Correspondence to: Maisa Ribeiro, Department of Medicine, Mineiros University Center, Mineiros, Brazil, E-mail: maisaribeiro22@outlook.com

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Moreover, numerous studies have explored the therapeutic potential of Mesenchymal Stem Cells (MSCs) and their secretions, such as exosomes [10,11]. Understanding the mechanisms of repair not only facilitates the integration of stem cell therapy with other approaches in burn wound healing but also aids in the translation of stem cell-based therapies from laboratory settings to clinical practice.

LITERATURE REVIEW

Stem cells, characterized by their molecular multipotency and the ability to differentiate into various cell lineages under specific conditions, present a potential avenue for tissue repair and regeneration. Their capacity for self-renewal, proliferation, and specialization has led to the exploration of innovative therapeutic approaches for treating a wide array of systemic diseases, injuries, fractures, inflammations, necrosis, neoplasms, and age-related tissue losses. *In vitro*, MSCs can be guided to differentiate along multiple phenotypic pathways by growth factors and substances such as pedestal-specific media, indomethacin, hydrocortisone, and Transforming Growth Factor β (TGF-β). *In vivo*, stimuli such as tissue damage from trauma, fractures, inflammation, necrosis, and tumors can directly mobilize MSCs to differentiate into connective tissue cells [12].

In terms of cell sources, various types of stem cells, particularly Mesenchymal Stem Cells (MSCs), derived from different origins have been extensively studied in models for burn wound repair. These include Bone Marrow-Derived MSCs (BM-MSCs), umbilical cord blood MSCs, adipose-derived stem cells, amniotic membrane-derived MSCs, amniotic epithelial MSCs, and hair follicle stem cells [13]. However, BM-MSCs and adipose-derived stem cells are predominantly utilized in burn wound repair. Studies have demonstrated that transplantation of BM-MSCs and similar counterparts promotes vascularization through the secretion of cytokines, such as fibroblast growth factors and vascular endothelial growth factor, to recruit cells and facilitate burn wound healing. Additionally, stem cells function by upregulating the expression of tumor necrosis factor to suppress the expression of factors like prostaglandin E2 and TGF-β1, thereby reducing the inflammatory response [14].

Furthermore, stem cells can be broadly categorized into two types Adult Stem Cells (ASCs) and Embryonic Stem Cells (ESCs). While ESCs exhibit greater potential for differentiation, classified as totipotent and pluripotent, their utilization in cell therapy and research is constrained by issues of histocompatibility, safety, and ethical concerns. As a result, ASCs have become a focal point of study in regenerative medicine [15]. ASCs can be isolated and characterized from various organs, including the brain, tooth pulp, adipose tissue, and primarily, bone marrow and umbilical cord. Although ASCs are considered multipotent, capable of differentiating into specific tissue types, particularly those in proximity to their source, they play an important role in tissue homeostasis [8]. Thus, ASCs are favored in cellular therapy due to their ease of acquisition, high proliferation and differentiation capacity, autologous use potential, simple laboratory manipulation, low immunogenicity, integration into host tissue, and interaction with the surrounding environment [9].

Bone marrow transplants have long been utilized in regenerative medicine for treating various diseases affecting the hematopoietic system [14]. However, with advancements in medical science, umbilical cord and placental blood have emerged as alternative sources of ASCs, offering advantages such as complete compatibility between donor and recipient, reduced risk of immune incompatibility, and increased availability compared to bone marrow banks [16].

Although bone marrow and umbilical cord remain primary sources of ASCs, their utilization is limited due to donor scarcity and the challenges associated with cell procurement. Consequently, adipose tissue has emerged as a promising source of ASCs for therapeutic applications, offering advantages such as easy access, simple isolation procedures, abundant availability through liposuction, and minimal donor morbidity. Furthermore, stromal cells derived from adipose tissue exhibit comparable potential to differentiate into mesodermal-origin cells and tissues, presenting a favorable alternative in the procurement process [17].

Adipose tissue comprises two types White Adipose Tissue (WAT) and Brown Adipose Tissue (BAT). While BAT is found in small quantities in adult humans, WAT plays a significant role due to its abundance of multipotent stem cells responsible for continuous tissue renewal [18]. Fractionation of adipose tissue allows the isolation of the Stromal Vascular Fraction (SVF), comprising a diverse pool of cells including mature adipocytes, pre adipocytes, fibroblasts, vascular smooth muscle cells, endothelial cells, monocytes, macrophages, lymphocytes, and Adipose tissue-Derived Stem Cells (ADSCs) [17].

ADSCs derived from the Stromal Vascular Fraction (SVF) exhibit a greater abundance and higher proliferation rate compared to ASCs derived from bone marrow stroma (ASC-MO). According to Torres FC, et al. [19], approximately 2 to 3 × 10^8 Canadian Triage and Acuity Scale (CTAs) can be obtained from every 300 mL of collected adipose tissue, while material extracted from bone marrow can generate only one CTA for every 10^5 stromal cells. Furthermore, ADSCs have the capability to differentiate *in vitro* into multiple lineages, not only mesenchymal such as adipocytes, chondrocytes, osteoblasts, neuronal cells, endothelial cells, and cardiomyocytes but also into tissues of non- mesenchymal lineage, a phenomenon known as trans differentiation [19]. However, there may be differences in ADSC proliferation and differentiation characteristics during *in vitro* cultivation compared to *in vivo* conditions [18].

Recently, Mesenchymal Stem Cells (MSCs) have seen widespread application in promoting wound healing across various skin conditions, particularly in cases of skin burns [13]. The therapeutic efficacy of MSCs can be attributed to their capacity for, differentiation, regeneration and exosome secretion. These exosomes typically range from 10 to 100 nm in size and contain high number of bioactive molecules such as proteins, mRNA, and microRNA (miRNA). MSC-derived exosomes are capable of being transferred to cells and the surrounding microenvironment, where they regulate cellular behavior and modulate targeted gene expression [20]. MSCs contribute to burn wound healing primarily through three

phases: Inflammation, proliferation, and maturation. During the inflammation phase, MSCs play a crucial role in modulating the immune response, thereby accelerating the healing process and suppressing pathological scar formation. They achieve this by regulating the polarization of macrophages towards the anti-inflammatory M2 phenotype and by inhibiting the proliferation of activated helper T cells, leading to a shift from a pro-inflammatory to an anti-inflammatory environment. Additionally, MSC exosomes exert an anti-inflammatory effect by downregulating pro-inflammatory enzymes and cytokines [21].

RESULTS AND DISCUSSION

In the proliferation phase, MSC exosomes facilitate angiogenesis and wound contraction by delivering miRNAs to endothelial cells, thus promoting blood vessel formation. Furthermore, they regulate fibroblast proliferation and migration, as well as keratinocyte proliferation and migration, essential for wound closure and re-epithelialization [22]. In the maturation phase, MSCs promote wound healing by enhancing specific Extracellular Matrix (ECM) events and collagen synthesis. They also inhibit excessive scar formation by suppressing myofibroblast formation and ECM sedimentation. MSC exosomes contain bioactive proteins and miRNAs that further contribute to inhibiting scar formation, thus aiding in wound healing [23].

Overall, MSC-based therapy, particularly through the use of MSC exosomes, holds significant potential in promoting burn wound healing by regulating various cellular processes across different phases of wound repair. Thus, injection of stem cells not only accelerates the healing process of burn wounds but also effectively dampens inflammation and facilitates skin function recovery through the action of cytokines secreted by the stem cells, thus establishing a conducive microenvironment for repair [21].

In efforts to characterize and isolate ASCs more specifically, studies aim to identify surface markers. However, due to the challenge of defining a single specific antigen, the international society for cellular therapy proposed minimum criteria including the capacity to adhere to culture flasks, multipotent differentiation potential towards chondrogenic, adipogenic, and osteogenic lineages, expression of mesenchymal surface markers ((Cluster of Differentiation) CD105, CD73, and CD90), and absence of hematopoietic endothelial markers (CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR).

Characterization studies have demonstrated similarities in surface markers between ADSCs and ASC-M populations expressed during *in vitro* cultivation. For example, Sullivan MO, et al. [24], observed high expression rates for $CD90^{+}$, $CD44^{+}$, and $CD45^{-}$ in cells collected from adipose tissue, despite these markers being characteristic of bone marrow-derived SC, once this cell populations can be easily identified and quantified through the expression of surface immunomarkers. Hematopoietic SCs typically express the CD34 antigen, while MSCs lack specific markers. Similarly, Riccobono D, et al. [25], found positive expression for $CD90^{+}$, $CD44^{+}$, and negative expression for CD45 in cells derived from adipose tissue. Fraser JK, et al. [26], demonstrated *via* flow cytometry analysis, that ADSCs express cell surface markers similar to those expressed by MSCs, including CD105, SH3, Stro-1, CD90, and CD44, while not expressing the hematopoietic marker CD45 or the endothelial marker CD31. Additionally, ADSCs express CD49d while MSCs express CD106, allowing for the differentiation between these two populations.

ADSC immunophenotyping studies have shown that the expression of surface biomarkers can vary during cell culture expansion, potentially influenced by plastic adhesion and proliferation in high concentrations of Fetal Bovine Serum (FBS), leading to less homogeneous cultivation [27]. Thus, a more appropriate method of isolating ADSCs directly after obtaining the SVF or its *in vitro* expansion would ensure a higher degree of purity compared to selection solely based on adherence to plastic [27].

Moreover, therapy based on MSCs has been proven to be safe and effective in improving granulation formation, promoting new vessel formation, enhancing re-epithelialization, reducing scar formation, and mitigating side effects such as pain, infection, and blistering [21-23]. Although previous studies have demonstrated favorable outcomes of MSC-based therapy in burn wound healing, only one study has investigated the immunomodulatory effects of MSCs, as highlighted in preclinical research [27]. Additionally, among the 12 studies listed on the clinical trials data bank website, few have reported their results, with only one study disclosing a reduction in side effects. This scarcity of reported efficacy could be attributed to limited patient numbers and short follow-up durations [28].

CONCLUSION

In conclusion, burn injuries represent a significant global health concern, necessitating effective treatment strategies to address their debilitating consequences. Current approaches, including debridement, skin grafts, and silicone therapy, have limitations in achieving optimal outcomes. Stem cell therapy, particularly utilizing Mesenchymal Stem Cells (MSCs), holds immense potential in enhancing natural skin regeneration processes and improving burn wound healing. Despite challenges such as protocol standardization and long-term follow-up, MSC-based therapy has shown encouraging results in promoting granulation formation, angiogenesis, and scar reduction. Further research is essential to elucidate underlying mechanisms, optimize treatment protocols, and translate stem cell-based therapies into clinical practice effectively. With ongoing advancements in stem cell research and therapeutic applications, there is a considerable opportunity to revolutionize burn injury management and enhance patient outcomes on a global scale.

REFERENCES

1. Raaijmakers MH. Overview of Stem Cells. 2019.
2. Roeder RA, Schulman CI. An overview of war-related thermal injuries. J Craniofac Surg. 2010;21(4):971-975.
3. Hettiaratchy S, Dziewulski P. Pathophysiology and types of burns. Bmj. 2004;328(7453):1427-1429.

4. Francis E, Kearney L, Clover J. The effects of stem cells on burn wounds: A review. Int J Burns Trauma. 2019;9(1):1.
5. Cruz S, Calfa A. Epidemiological survey of burns in children less than six years in age admitted to the Corporation for Aid to Burned Children (COANIQUEN) in Antofagasta, Chile. Rev Cienc Salud. 2001;5(1):17-26.
6. Cheng JZ, Farrokhi A, Ghahary A, Jalili RB. Therapeutic use of stem cells in treatment of burn injuries. J Burn Care Res. 2018;39(2): 175-182.
7. Singh VK, Kumar N, Kalsan M, Saini A, Chandra R. Mechanism of induction: Induced Pluripotent Stem Cells (iPSCs). J Stem Cells. 2015;10(1):43.
8. Wang L, Wang L, Huang W, Su H, Xue Y, Su Z, et al. Generation of integration-free neural progenitor cells from cells in human urine. Nat Methods. 2013 ;10(1):84-89.
9. Xue Y, Cai X, Wang L, Liao B, Zhang H, Shan Y, et al. Generating a non-integrating human induced pluripotent stem cell bank from urine-derived cells. PloS one. 2013 Aug 5;8(8):e70573.
10. Gowen A, Shahjin F, Chand S, Odegaard KE, Yelamanchili SV. Mesenchymal stem cell-derived extracellular vesicles: Challenges in clinical applications. Front Cell Dev Biol. 2020;8:149.
11. Zhu Q, Li Q, Niu X, Zhang G, Ling X, Zhang J, et al. Extracellular vesicles secreted by human urine-derived stem cells promote ischemia repair in a mouse model of hind-limb ischemia. Cell Physiol Biochem. 2018;47(3):1181-1192.
12. van der Veer WM, Bloemen MC, Ulrich MM, Molema G, van Zuijlen PP, Middelkoop E, et al. Potential cellular and molecular causes of hypertrophic scar formation. Burns. 2009;35(1):15-29.
13. Lim JS, Yoo G. Effects of adipose-derived stromal cells and of their extract on wound healing in a mouse model. J Korean Med Sci. 2010;25(5):746.
14. Julsgaard M, Christensen LA, Gibson PR, Gearry RB, Fallingborg J, Hvas CL, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. Gastroenterology. 2016;151(1):110-119.
15. Dreifke MB, Jayasuriya AA, Jayasuriya AC. Current wound healing procedures and potential care. Mater Sci Eng C Mater Biol Appl. 2015;48:651-662.
16. Shumakov VI, Onishchenko NA, Rasulov MF, Krasheninnikov ME, Zaidenov VA. Mesenchymal bone marrow stem cells more effectively stimulate regeneration of deep burn wounds than embryonic fibroblasts. Bull Exp Biol Med. 2003;136:192-195.
17. Tabit CJ, Slack GC, Fan K, Wan DC, Bradley JP. Fat grafting versus adipose-derived stem cell therapy: Distinguishing indications, techniques, and outcomes. Aesthetic Plast Surg. 2012;36:704-713.
18. Walgrave S, Zelickson B, Childs J, Altshuler G, Erofeev A, Yaroslavsky I, et al. Pilot investigation of the correlation between histological and clinical effects of infrared fractional resurfacing lasers. Dermatol Surg. 2008;34(11):1443-1453.
19. Torres FC, Rodrigues CJ, Stocchero IN, Ferreira MC. Stem cells from the fat tissue of rabbits: An easy-to-find experimental source. Aesthetic Plast Surg. 2007;31:574-578.
20. Kim S, Lee SK, Kim H, Kim TM. Exosomes secreted from induced pluripotent stem cell-derived mesenchymal stem cells accelerate skin cell proliferation. Int J Mol Sci. 2018;19(10):3119.
21. Wang M, Xu X, Lei X, Tan J, Xie H. Mesenchymal stem cell-based therapy for burn wound healing. Burns & trauma. 2021;9:tkab002.
22. Regmi S, Pathak S, Kim JO, Yong CS, Jeong JH. Mesenchymal stem cell therapy for the treatment of inflammatory diseases: Challenges, opportunities, and future perspectives. Eur J Cell Biol. 2019;98(5-8): 151041.
23. Velnar T, Bailey T, Smrkolj V. The wound healing process: An overview of the cellular and molecular mechanisms. J Int Med Res. 2009;37(5):1528-1542.
24. Sullivan MO, Gordon-Evans WJ, Fredericks LP, Kiefer K, Conzemius MG, Griffon DJ. Comparison of mesenchymal stem cell surface markers from bone marrow aspirates and adipose stromal vascular fraction sites. Front Vet Sci. 2016;2:82.
25. Riccobono D, Agay D, Scherthan H, Forcheron F, Vivier M, Ballester B, et al. Application of adipocyte-derived stem cells in treatment of cutaneous radiation syndrome. Health Phys. 2012;103(2):120-126.
26. Fraser JK, Wulur I, Alfonso Z, Hedrick MH. Fat tissue: An underappreciated source of stem cells for biotechnology. Trends Biotechnol. 2006;24(4):150-154.
27. Ribeiro M, Santos KC, Macedo MR, de Souza GA, de Assis Neto FI, Araujo GH, et al. Use of adipose derived stem cells accelerates the healing process in third-degree burns. Burns. 2024;50(1):132-145.
28. Ullah S, Mansoor S, Ayub A, Ejaz M, Zafar H, Feroz F, et al. An update on stem cells applications in burn wound healing. Tissue and Cell. 2021;72:101527.