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Study Literature: Role of Secretome Mesenchymal Stem Cell as Innovation in Burn Treatment

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Abstract
The purpose of this review was to determine the role of MSCs in burn management. Scientific publication databases such as Researchgate, Google Scholar, ScienceDirect, and Pubmed were used for literature searches. [(Secretome, Mesenchymal stem cell Adipose Tissue, Umbilical Cord, Bone Marrow) AND (Burn wound OR wound healing OR burn injury OR thermal injury)] are the keywords used. In ten studies, rats, mice, and humans were used as research subjects in randomized clinical trials to conduct synthetic analyses. MSC therapy involves the use of bone marrow, cord blood, and adipose tissue. MSC therapy heals burns by suppressing the inflammatory response and oxidative stress, stimulating angiogenesis, and causing closure and repair (remodeling). MSC therapy has also been shown to reduce scarring and contracture formation.

Keywords:
Secretome; Mesenchymal stem cell Adipose Tissue; Burn wound; Wound healing, Scar Tissue

INTRODUCTION

Burns is still a problem in the health care system because of the morbidity and mortality they cause. Burns can also disrupt daily activities, and in severe cases, they can result in dependency on others, loss of work, and permanent tissue damage. According to ABA data [1] the incidence of burns most often occurs in degree II 78% while degree I is only 10% and 17% in degree III. Although burn-related deaths have decreased in recent years due to technological advances, major challenges in burn management and healing remain [2].

If patience gets a burn, the burned area of your skin will affect the epidermis, dermis, and subcutaneous tissue. This is determined by the cause and the length of time the skin is in contact with the cause. The depth of the burn will affect skin integrity, cell death, and contractures, which will limit the patient's joint movement [3].

In addition to joint contractures patients with severe burns will typically experience severe dehydration, electrolyte imbalance, and severe pain [4]. Typically, patients who experience the above will be treated for burns with skin grafts, but this treatment takes a long time to heal [4]. Treatment in this manner has the disadvantage of causing scarring, and for female patients, it will affect the patient's psychology due to unsatisfactory cosmetic results [4], [5]. In using MSC secretome, the main target is accelerating wound healing in each phase of waound healing by helping to stimulate growth factors around the wound environment [11].

As a result, advancements and innovations in burn treatment are urgently needed to accelerate burn healing and produce satisfactory therapeutic outcomes for patients. Now, stem cell therapy is thriving. Mesenchymal Stem Cell (MSC) is one of the most widely developed stem cells[4], [6], [7].

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MSC is a type of stem cell that can differentiate into epidermal cells and can be isolated and developed from a variety of sources in the body, including the umbilical cord, bone marrow, and adipose tissue. The disadvantage of using MSC is that it must be stored at -80^{0}C and must be applied by an expert [11].

As a result, innovation in the use of MSC continues to develop, and a method to facilitate the use of MSC is discovered, namely by using a medium for culturing and growing MSC, or what is known as Sekretome (Conditioned Medium).

The secretome is secretions from stem cells as well as MSCs that grow in culture media and resemble the MSC itself, which has the same growth factors as MSC like VEGF, TGF-β, etc. The main benefit of the secretome is that it can be stored in the freezer and easily made into a preparation, making it easier to apply stem cells. According to Ratih et al, the stability of the frozen secretom reaches a limit of up to 1 year and the finished drug after the first use is up to 2 months after the drug seal is opened, making it easier to aplly stem cell [11].

Secretome MSC is said to be capable of accelerating tissue re-epithelialization and remodeling, as well as inhibit cell apoptosis and inflammatory responses [4], [5].

In animal studies, secretome MSC has the potential to effectively accelerate wound healing. In rats and mice, secretome MSC has been shown to reduce burn area [8]–[10].

As a result, this article will go over the use of Secretome MSC for an innovation in burn treatment.

METHOD

Scientific publication databases such as Researchgate, Google Scholar, ScienceDirect, and Pubmed were used for literature searches. [(**Secretome, Mesenchymal stem cell Adipose Tissue, Umbilical Cord, Bone Marrow) AND (Burns OR wound healing OR burns OR thermal injury**)] were the keywords used.

The first stage involved filtering literature obtained from online database searches using predetermined keywords. Following that, all irrelevant titles will be removed. The manuscripts are then determined to be included in the analysis using inclusion and exclusion criteria in the second stage.

Articles that contain the keywords mentioned are eligible for inclusion. As well as the exclusion criteria, which are articles that do not contain the keywords mentioned. Furthermore, the literature sources that have been chosen and meet the inclusion criteria are thoroughly read and analyzed in order to extract the essence of the literature.

The narrative synthesis incorporates all literature sources relevant to the role of MSC in burns. This review, as a qualitative study, attempts to explain the findings of MSC's role in burn treatment. Starting with an overview of their mechanism of action, narrative synthesis was used to reach conclusions about the use of mesenchymal stem cells as burn therapy.

RESULT AND DISCUSSIONS

This literature review discovered 38 articles that met the inclusion criteria. Table 1 shows how MSC secretome therapy derived from various cells aids in the healing of burns.

Table 1. Articles with inclusion criteria (4)

Disease	Subject	Source secretome	Results	Reference
Third degree burns	Mouse	ADSC-CM	Wound closing ↑Hair growth	[11]
Second degree burns	Mouse	BMSC-CM	Wound closing ↑collagen formation Proliferation is formed	[12]
wound healing	Mouse	UCSC-CM	tissue regeneration	[13]

Burn wound	Mouse	BM Tikus	tissue regeneration	[8]
Third degree burns	mice	BM Mencit	novel adjuvant therapy	[14]
Wound healing	in vivo in vitro	ADSC-CM	significant wound healing	[15]
Wound healing	in vitro	MSC	Dermal fibroblasts and keratinocytes grow	[16]
Wound healing	mice	ADSC-CM	wound healing	[17]
Wound healing	mice	ADSC-CM	CM Spheroid is better than Monolayer Wound closing Proliferation is formed	[18]
Burns	clinical trials (human)	ADSC-CM	wound healing	[19]

Wound healing is a complex process that includes the hemostatic, inflammatory, proliferative, and remodeling phases. The development of a method of treatment with mesenchymal secretome from stem cells can facilitate and accelerate the four wound healing processes.

The mesenchymal stem cell secretome can be derived from a variety of tissues, both embryonic and adult, and can differentiate into a variety of cell types. Mesenchymal secretions can be derived from the umbilical cord, bone marrow, or adipose tissue in burn healing therapy. Several previous research findings support this.

Kim et al., [15] investigated MSCs derived from adipose tissue in vivo and in vitro. The purpose of this study is to look at the effects of HDFs (Human Dermal Fibroblasts) that were analyzed using ELISA and RT PCR, while the in vivo test used 6 mice that were given wounds with a diameter of 7 mm and then divided into two groups. The first group received a collagen gel solution, while the second group received a collagen gel solution plus $1x10^6$ ADSC. The wound diameter was measured after 7 days, and histological tests were performed on day 21. The combined collagen + ADSC gel solution had a significant effect on wound healing, according to the findings.

Walter et al., [16] conducted a study in 2010 to observe the degree of wound closure using image capsular microscopy and a digital camera. The parameters of the number of L929 and AHCAT cells were monitored in this study using the Cell LQ automated cell counting and tracking protocol (chip-man technologies). According to the findings of this study, the effect of closing wounds on the skin with MSC produced satisfactory results because MSC stimulated dermal fibroblasts and keratinocytes to grow rapidly.

In addition to using in vivo and invitro tests in MSC research as a burn remedy, Zhou et al. [19] reported the use of CM-ADMSC in wound healing in humans who experienced re-injury after the layer removal process outer skin (FXCR). In this study, 19 people participated as respondents. Following the FXCR procedure on the inner arm, CM-ADMSC was applied topically. Respondents were divided into two groups: those who received ADMSC and those who received FBS. Erythmia, melanin, TEWL, and elasticity were among the parameters measured. On days 1, 4, 7, 14, and 21, tests were performed. On days 1, 4, 7, 14, and 21, tests were performed. According to the findings of this study, ADMSC is an effective method for wound healing following the FXCR process, as it reduces the side effects of arrhythmia and hyperpigmentation.

Bhang et al., [17] conducted another study in which they injected 200 L of CM-ADMSC, $2x10^6$ cells into mice for 7 days. M-RNA expression of SM-actin and CD31 were used as parameters. After that, immunohistochemistry, transplantation of PKH26-labeled BMMNCS, and Lose Doppler imaging analysis were performed. The results show that CM has a much better effect on wound healing than transplantation therapy.

Kawai et al., [13] conducted a study on several rats and observed the parameters of the MSC growth factor using in vitro tests using ELISA analysis to see growth factors and also using R-PCR analysis to express osteogenesis and angiogenesis before moving on to in vivo tests with test animals being treated for 2 weeks with MSC injection and then subjected to histological tests. The findings of this study suggest that several cytokines found in UMCM-MSC play a role in the regeneration of injured tissue.

In 2015, Kwon et al., [18] conducted a study with mice objects divided into four groups: control, Fresh Medium (FM), Spheroid CM, and Monolayer CM, which came from two CM media. This study used Elisa analysis to look at growth factors (H-VEGF, HGF, FGF2, and SDF-1 α) in the R&D system in Minneapolis. The parameters examined in the in vivo test are histology, immunohistochemistry, PCR, and Western blot analysis, and the parameters examined are dermal and epidermal from wound healing. According to the findings of Kwon's study, Spheroid CM was more effective for wound healing than the other treatment groups.

Another study, conducted by Aryan et al., [12] on 32 rats given burn intervention for 28 days with parameters: stereological and immunohistochemistry analysis, revealed significant results with increased proliferation rates, increased collagen formation, and increased angiogenesis in the affected area.

The following study by Abbas et al., [8] used Wistar rats that were divided into three treatment groups: control, placebo, and MSC. Each group was treated with wounds for 72 hours. Following that, histochemistry, immunohistochemistry, and RT-PCR tests, as well as scintigraphy, were performed. The results of the various analyses show that the percentage of tissue repair from the MSC test group is higher than that of the other groups.

Meanwhile, in the study of Alapure et al., [14] MSC were made in a hydrogel preparation called ACgels and were tested on mice with third-degree burns and were given an injection of the preparation as much as $1X10^5$ or the medium was as much as 30 L after one day and obtained The results demonstrated that MSC-seed ACgels provided a novel adjuvant therapy for burns while exhibiting no toxicity.

Laksmitawati et al., conducted a recent study on 32 rats that received dorsal burn intervention. The rats were separated into four groups: placebo, CM, Silver Sulfadiazine, and no treatment. The intervention lasted 21 days, with daily parameters such as test wound diameter, scab formation, blister formation, and hair growth. The findings of this study revealed that AD-CM produced results and faster hair growth in the wound area [11].

MSC therapy aids burn to heal and reduce the risk of scarring in all studies included in this systematic literature review synthesis analysis. Furthermore, no study discovered any significant side effects such as neoplastic activity or an exaggerated immune response. These findings imply that MSC therapy may be a promising regenerative therapy for burn treatment [2] [4].

Mesenchymal stem cells promote wound healing and skin regeneration by promoting granulation tissue formation, modulating inflammation, regulating extracellular matrix repair, and contributing to fibroblast repair. The process involves paracrine signaling,

discharge angiogenesis, immunomodulation, endogenous stem cell recruitment, and differentiation [2].

Furthermore, mesenchymal stem cells can significantly increase collagen, fibronectin, and elastin fibroblast production, enhancing extracellular matrix repair. Mesenchymal stem cells can modulate the inflammatory response, accelerate extracellular matrix remodeling by stimulating increased collagen production, increase epidermis thickness through accelerated epithelialization, and increase fibroblast and keratinocyte migration, thereby accelerating wound closure [4].

CONCLUSION

Mesenchymal stem cells are adult stem cells that can be isolated from a variety of human tissues, including the umbilical cord, spinal cord, and adipose tissue. The study of obtaining mesenchymal stem cells plays a role in efforts to accelerate burn wound healing via various mechanisms such as reducing the inflammatory phase, accelerating proliferation formation, and accelerating the remodelling phase of injured tissue. Mesenchymal stem cells have the potential to be developed as part of the wound and burn therapy.

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