
بسم الله الرحمن الرحیم

The Use of Mesenchymal Stem Cells in Burn Wound Healing

Research Presentation

By Arad Kianoush

- A myriad of studies using stem cells are being done with promising results in various fields ranging from oncologic and hematologic diseases to organ transplants and wound healing. In the field of wound healing, the use of different types of stem cells has been reported for different types of wounds.
- Burn wounds have proven to be capable of having a devastating effect both functionally and cosmetically, necessitating the search for a better and more efficient cure.
- Today’s main topic will be stem cells and their application in clinical medicine, especially WJ-MSCs (Wharton Jelly-Mesenchymal Stem Cells).

- Stem cells are undifferentiated pluripotential cells that are capable of producing other types of cells, including new stem cells identical to mother cells.
- Stem cells can be of embryonal origin or adult origin, depending on the type of tissue they are derived from.
- Embryonal stem cells are derived from either embryonal tissue or from germ cells in adults. On the other hand, adult stem cells are derived from adult tissues of different organs, especially those with a high turnover rate such as intestines and bone marrow.

- Stem cells have been implicated in the healing of wounds in general. However, the methods of application of the stem cells in burn wound healing are diverse, including topical application, local injection, intravenous or systemic injection, and dermal or carrier application.
- The application of stem cells in wounds promoted more efficient reepithelialization by their proliferative effect on keratinocytes. Moreover, this effect of stem cells was found to be mediated by keratinocyte growth factor1 (KGF-1) and platelet derived growth factor-BB (PDGFBB).

- Amniotic fluid derived stem cells have also been used in wound healing. Skardal et al. tested the effect of amniotic fluid derived stem cells in wound healing in a mouse model. Wound closure, reepithelialization, and angiogenesis were more rapid in mice treated with the stem cells in comparison to those treated with fibrin collagen gel only. Additionally, stem cells did not integrate permanently in the tissue, thus, suggesting that their effect is due to released factors and not by direct interaction.

- Focusing on the role of cytokines in burn wound healing, Payne et al. studied the role of amnion derived cellular cytokine solution. In the study, Payne et al. used amnion derived multipotent progenitor cells to harvest cytokines and apply them in burn wound healing. Amnion derived cellular cytokine solution showed statistically significant improvement in the epithelialization of the burn wounds and the appearance of hair growth compared to controls. In addition, the results demonstrated a faster epithelialization in burn wounds with increased frequency of application of the cytokines, further strengthening the role of stem cell derived cytokines in burn wound healing

- More recent studies have also highlighted the role of stem cells in the process of wound healing in general and burn wound healing in specific. Koenen et al. isolated acute wound fluids and chronic wound fluids and compared their effects on adipose tissue derived stem cell function in wounds. They came to the conclusion that acute wound fluids had a positive effect on the proliferation of adipose derived stem cells in wounds while chronic wound fluids had a negative effect; the mentioned findings might explain the insufficient and slow healing process in chronic wounds due to a stem cell deficiency.

- The process of burn wound healing involves different types of growth factors, receptors, and cytokines. These factors are related to stem cell homing, differentiation, and proliferation. Additionally, when applied to burn wounds, they led to a better and faster healing process.
- The use of stem cells for burn wound healing, as reported in the literature, dates back to 2003 with Shumakov et al.. Shumakov et al. were the first to use mesenchymal bone marrow derived stem cells (BMSC) in burn wound healing and compared them to embryonic fibroblasts. The experiments were done on rats where mesenchymal bone marrow derived stem cells were applied to wounds showing decreased cell infiltration of the wound and an accelerated formation of new vessels and granulation tissue in comparison with embryonic fibroblasts and controls (burn wounds with no transplanted cells). Hence, this study marked a new era in the research of burn wound healing by being the first to test the use of stem cells in this complex process.

- In 2004, Rasulov et al. were the first to report using bone marrow mesenchymal stem cells in humans; a female patient with extensive skin burns (IIIB 30% of body surface area) had the stem cells applied onto the burn surface. The application of stem cells caused faster wound healing and active neoangiogenesis. Another study done by Rasulov et al. on rats also showed the superiority of stem cells in burn wound healing. In the rat study, the application of mesenchymal stem cells on burns reduced cell infiltration, improved neoangeogenesis, and reduced the formation of granulation tissue

- Stem cells have attracted many controversial public opinions over time. Many people argue that embryonic stem cell harvesting would be done by killing embryos which would be unethical. Others would argue that even if embryos are used for stem cell research, it is not wrong. However, the path that this may lead to would be wrong such as embryo “production” for research purposes. The public view towards the therapeutic use of stem cells has become more tolerant over time. The role of educating people about the colossal potential for the use of stem cell has thus proven beneficial. People are now more educated about the different sources of stem cells and have become supportive of their use. Regarding the acceptance of stem cells as an efficient therapy for burn wound healing in specific, a study done by Clover et al. showed a very positive opinion. The biggest majority of people were willing to accept autologous stem cells, though a big percentage was also welcoming the idea of using allogeneic stem cells.

- WJ-MSCs have also been broadly studied as a promising source for skin wound healıng. For example, as described by Azari et al. (2011) in their article, caprine WJ-MSCs showed complete re- epithelialization of the wounds with minimum inflammation and scar formation on Day 7. However, no complete epithelialization was observed in the untreated control group after 12 days. Administration of human WJ-MSCs has also improved wound healing in an excisional full-thickness skin murine model through enhancing re- epithelialization, vascularization, proliferation, survival, and migration of skin fibroblasts (Arno et al., 2014). An animal model of burn has also been employed to confirm the potential of WJ-MSC therapy in this pathology. Subcutaneous injection of the WJ-MSCs suppressed secondary inflammation via reducing inflammatory cytokines and, therefore, promoted burn healing process and skin repair in rat burn models (Zhang et al., 2015). Sun, Zhang, Song, Zhu, and Zhu (2019) assessed the healing effects of these MSCs in radiation- induced skin injury in rats. They found that WJ-MSCs improved wound healing quality by promoting cell proliferation, sebaceous glands regeneration, and angiogenesis.

- In brief, the use of stem cells in burn wound healing appears to be very promising. While most studies were performed on animals, the application to humans is yet at its start. Hence, what is needed is more studies. Additionally, the signaling pathways followed by stem cells involved in the burn wound healing along with their factors and signals constitute a very dynamic and promising research field.

Thank You