

## Review (Narrative)

# Use of Stem cells in Burn Wound Healing

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**SUMMARY**

Stem cell research can open gateways to further development in science changing the way of healing process. It can prove to be a game changing factors both practitioners of medicine and patients. Patients suffering from burn wounds no longer have to face aesthetic issues when wounds are healed and the healing process will become more rapid and effective. More focus needs to be done on analyzing the way a body of experiments and their conclusions will affect humans since most of the trials have used animals as subjects. Controversial opinions regarding the use of stem cell research is presenting itself as a major hindrance in its application. To counter this, more awareness needs to be created amongst the general public regarding the ways in which stem cell research can be done. Adult cells can also be used to generate stem cells; hence the argument that embryos will be harmed in generating stem cells is futile. It is also important to note that some of the experiments have failed to provide consistent results, which need to be reviewed in order to see their feasibility in being applied to humans and provides an opportunity for stem cell researchers to take it up as a challenge.

**KEYWORDS** Burn wound; Stem cell; Inflammation; Regeneration; Proliferation

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## INTRODUCTION

Stem cell therapy and its uses can prove to be of immense benefit for the field of science. Stem cell studies are providing promising results in various fields ranging from oncological to hematologic and spreading as far as organ transplant and wound healing. Different kinds of stem cells can be made use of for repairing different kinds to wounds (1-3). The exorbitant amounts of burn wounds suffered by people, especially in the Middle Eastern region-specifically those facing armed conflicts; make these types of wounds require special attention. The search for an improved cure is necessary because burn wounds have a severe functional and an over whelming aesthetic effect on people. Considering that stem cells is the most sought after field of research with continuous updates and studies, it became necessary that an updated review be maintained in addition to experimental studies in order to include the recent developments in burn wound healing with the use to stem cell research.

Stem cells are inherently pluripotent cells, which are undifferentiated and have the capability to generate other kinds of cells which also include new stem cells identical to the mother cell (4). Whether stem cells have an adult or embryonic origin depends on the tissue they are derived from. Embryonic stem cells can be derived from embryonal tissue or from germ cells found in adults. Adult stem cells, on the contrary are derived from tissues of several different organs in adults especially intestines and bone marrow since they have a higher turnover rate.

## WOUND HEALING

Stem cells can be applied to the wound for the purpose of healing in multiple ways including local injection, topical application, intravenous or systemic injection and dermal or carrier application. The feasibility of stem cells in promoting rapid and improved healing has been proven by several studies. In a study conducted by Alexei (5), Adipose derived mesenchymal stem cells were used on mice for wound healing and the effect was compared with dermal fibroblasts. The application of stem cells led to effective reepithelialization of the wounds due to their proliferative effect on the keratinocytes. In addition, this impact of stem cells on the wounds was mediated by platelet derived growth factor BB (PDGF-BB) and keratinocyte growth factor-1 (KGF-1). Amniotic derived stem cells have also been made use of in the process of healing. Skardal (6) tested the effect of these kinds of stem cell in a mouse model. The results showed that wound closure, reepithelialization and angiogenesis were more rapid with mice treated with stem cells rather than fibrin collagen gel only. It was also observed that the stem cells did not amalgamate permanently with the tissue which suggests that their impact was due to

released factors and not by direct interaction. Another type of stem cells used in wound healing is the bone marrow derived mesenchymal stem cells. Leonardi (7) made use of these stem cells to provide wound healing in artificial dermal substitutes. It was observed that the stem cells increased vascular density in the wounds along with the rate of reepithelialization. Another study by Zhang (8) investigated the effect of activin signaling on the homing of stem cells to wound sites. The results indicated involvement of ERK and JNK signaling pathways in active signaling and eventually the homing of stem cells (8).

## Physiology of Burn Wound Healing

Several studies have been reported that indicate the physiology with which stem cells speed up the process of burn wound healing. Mansila (9) discovered that after severe burn wounds, there was an evidence of such cells in bloodstream that had similar phenotypes to mesenchymal stem cells leading to the conclusion that these stem cells can play an active role in promoting wound healing. Fox (10) found that there was an increased level of endothelial progenitor cells (bone marrow derived) in burns patients. The increased levels were proportional to the extent of the burn. Increased levels of angiogenic cytokines were also found which can be linked to the signaling pathway that is used for promoting the release of bone marrow derived stem cells. Payne (11) studied this impact of the role of cytokines further and observed the activity of amnion derived cellular cytokine solution. Amnion derived multipotent progenitor cells were used to extract cytokines and then apply them to the burned wound. The solution when applied showed considerable improvement in the healing process and also in the regrowth of hair compared to controls (11). Additionally, the greater the frequency of applying cytokines to the affected area, the faster the reepithelialization which strengthened the role of stem cells derived cytokines in burn wound healing.(11). A positive linear correlation between the total body surface area burnt and endothelial progenitor cell blood levels was found out by Foresta (12). Cabrera (13) went one step further and proposed that stem cells have an active role in healing by producing bioactive peptides such as thymosin 4 and others.

Koenen (14) separated acute and chronic wound fluids and compared their effect on adipose tissue derived stem cells and their function on burn wound healing. It was concluded that acute wound fluids had a positive impact on proliferation of adipose tissue derived stem cells whereas, a negative effect was observed with chronic wound fluids. The insufficient and slow healing process was the result of stem cell deficiency (14). Stem cells have also been shown to decrease dermal fibrosis development in burn wounds in mice (15). Decreased markers of myofibroblasts and down regulated type 1 collagen was observed with the skin cell treatment leading to a decrease in fibrosis that could have occurred to the skin (15). Hence the role of stem cells can

be extended to decreased fibrosis in burns and improved healing with less scar formation.

In short, growth factors, receptors and cytokines are the factors related to stem cell homing, differentiation and proliferation. When applied to burn wounds, they led to an improved and rapid healing process.

## Stem Cells and Burn Wound Healing

Literature regarding stem cells and burn wound healing can be traced back to 2003 with Shumakov (16) being the first one to use mesenchymal bone marrow derived stem cells as opposed to embryonic fibroblasts. Mesenchymal bone marrow derived stem cells were used on rat wounds showing decreased cell infiltration and rapid formation of new vessels and granulation tissues when compared with embryonic fibroblast. This was the first time stem cells were used in a complicated process and marked the beginning of a new era of research. Chunmeng (17) taking the research on step further did an analysis which proved that systemic transplantation of dermis derived multipotent cells promoted healing of wounds as opposed to no transplantation. Rasulov (18) became the first person in 2004 to test the mesenchymal cells on humans. The cells were applied on a female patient who had suffered severe skin burns, which led to faster wound healing and active neo angiogenesis. Another study by Rasulov showed the dominance of stem cells in healing (19). Mesenchymal cells were applied on rats Liu (20) performed experiments on pigs where collagen scaffolds with seeded mesenchymal cells were applied to the burns. Lataillade (21, 22) reported two cases where stem cells treated burn wounds. Mesenchymal stem cells were applied along with surgical excision, flaps and grafts to burn wounds of cutaneous radiation patients. Application of cells decreased inflammation and led to better healing. Dong (23, 24) inserted a vector of human beta defensin 2 into the stem cells, which showed a positive role for stem cells transfected with beta defensin 2 and also showed antibacterial properties.

When the stem cells were transfected with hepatocyte growth factor, the group treated with transfected stem cells depicted a larger range of reepithelialization starting the 1st week and continued up to the third week with thicker epidermis and lower content to collagen. Agay in the same year, performed experimental studies on pigs with cutaneous radiation by injecting intradermal mesenchymal stem cells which resulted in the gathering of lymphocytes to the wound with better vascularization compared to control. Riccobono studied the role adipose tissue derived stem cells in the treatment of cutaneous radiation. Autologous, allogeneic and acellular vehicles were grafted on to the burn wound areas. Autologous adipose derived stem cells resulted in better wound healing with no necrosis and less pain as compared to allogeneic stem cells.

The feasibility of porcine bone marrow derived stem cells along with skin-derived keratinocytes in healing of irradiated skin was studied by Yan. The effect on healing

was compared with a culture loaded with cells and one that was cell free. The culture with cells resulted in faster healing, epithelialization, angiogenesis and better granulation of the burn wound. Collawn treated them with dermal grafts with and without adipose derived stromal cells. The stromal cell containing grafts showed complete recovery of the epithelium after two days whereas, the cell free graft did not recover completely.

With reference to stem cells from human umbilical cords, a study investigated the effect of human umbilical cord derived mesenchymal stem cells in healing of severe burns inflicted in rats. Mesenchymal stem cells with fibrin glue and used it as a dressing for wounds. Scald wounds were inflicted on rats and the dressing was applied. Dressing with fibrin glue and stem cells in one group, fibrin glue only in the second, and no intervention in the third. After a month later, the treatment group with fibrin glue and stem cells showed relatively faster healing than the other two and had more proliferation of sebaceous glands.

Mice were inflicted with burns and the received stem cells injections and showed no significant difference in comparison to controls with respect to proliferation and vascularization. Nevertheless, the role of stem cells in burn wound healing is indeed a promising field and still requires extensive research.

## Stem Cells and Corneal Burn Wound Healing

Chemical burns of cornea are another area of study. Autologous limbal cells were utilized for ocular surface reconstruction of the contralateral eye which resulted in the creation of an improved corneal surface with betterment in vision and symptoms of the patients. Similar results were also found in other experiments that used limbal stem cells in inducing improvement of corneal healing and decreased neovascularization in both human and animal subjects. The therapeutic effect of mesenchymal stem cells in corneal chemical wound healing was studied by Mesenchymal stem cell media and mesenchymal stem cell culture media (without stem cells) reduced inflammation and promoted neovascularization of corneas (25). It was also observed that direct application provided better results than stem cell culture media. The use of cyclophosphamide to reduce inflammatory reactions and release bone marrow stem cells into circulation was observed and was given corneal alkali injuries to discover that rabbits with unsuppressed bone marrow have relatively greater reepithelialization of the corneas with clearer surfaces.

Role of bone marrow cells in improving the healing of corneal chemical wounds was brought about. In this study. Bone marrow derived cells were used to cure the alkali wounds on corneal surfaces of mice in a study conducted by Sel, and found that reepithelialization in the treated groups was faster than in the control group with no difference in corneal transparency. Soluble factors were the reason for the effect of the applied cells since stem cells and CD117+

cells were absent from the cornea after healing. Limbal cells were culture on fibrin and treated burn wounds to show that they promoted better healing now and also maintained the superior healing 10 years later in a study conducted by Rama. Stem cells also stimulated the formation of clearer corneal media in some experiments.

A series of studies performed in 2011 and 2012 by Basu analysed the use to limbal stem cells (26). In the first study application of limbal stem cells was followed by keratoplasty procedures, which resulted in good results, which were not compared with controls. In the second study, 66% of the patients that who failed primary procedures of corneal repair were exposed to secondary limbal stem cell transplant led to successful results with no neovascularization at a follow up of two years. Limbal biopsies from unaffected eyes were cultured on amniotic membranes as substrates further demonstrated the feasibility of allograft transplants, which resulted in, improved a vascular corneal healing without the need for immunosuppression (27). Biological factors that affected the role of stem cells in corneal burn wound healing was investigated by Pelligrini Important influence was of the accurate number of stem cells expressing p63 transcription factor.

## ALTERNATIVE THERAPIES IN BURN WOUND HEALING

Despite the fact that stem cells show great potential in curing burn wounds, alternative therapies need to be considered to further improve the treatment. For example, fat injections were used for severe burn wounds by Klinger to test whether the healing process is improved. The results depicted improvement in scars and tissue regeneration but the small population sample made the study limited. Role of keratinocytes was also investigated by Auxenfans, which resulted in a more rapid burn wound healing. Isolated stromal vascular fraction used by Atalay stimulated an increased in vascular endothelial growth factor and decreased the inflammation with better fibroblastic activity. Botox injections researched by Husein improved burn wound healing by increasing fibroblasts, TGF-B and TNF-alpha levels along with decreased inflammations. Heat shock protein 90 alpha also promoted faster healing and decreased inflammation.

Bone marrow, umbilical cord, adipose tissue or skin is the major sources from where stem cells are extracted. Debrided skin as a source of stem cells was used by Natesan. Hence, the adipose tissue from debrided skin of the wound can also be used as a source of stem cells. Natesan in another study also made use of isolated stem cells from debrided skin with collagen and fibrin based scaffolds. A better matrix deposition and epithelialization was observed due to decreased wound contraction with the use of these dermal equivalents. Mesenchymal stem cells from excised burn wound eschar was studied by van der Veen which showed

similar abilities to adipose derived stem cells in identifying the difference between osteocytes, chondroblasts and adipocytes.

Li investigated role of electric field in migration of stem cells, since endogenous electric fields are present in burn wounds naturally. The research proved that epithelial stem cells migrate to cathode in an induced electric field and this migration is proportional to the strength and duration of the field, involvement of mitogen activated protein kinase, PI3K and epidermal growth factor receptor. Therefore, in addition to stem cell, electric fields can also be applied to wounds to improve their migration.

Several pathways can be used to show the role of stem cells in burn wound healing including JNK and ERK 59 along with difference factors and mediators such as KGF-1 and PDGF-BB (28). This can also be done through released factors and not only by direct integration of stem cells into the wound scaffold or matrix (29). A potential enhancing role of stem cells as an aid in the healing process can be observed by their increased levels in the wounds (30). However, the results were found to be not 100 percent consistent. This can be because different experiments used different amounts of purified stem cells in differing phases of replication or differentiation in vitro. In short, these results analyses the healing process with stem cells qualitatively rather than quantitatively. More studies need to be done to evaluate the performance on a quantitative basis and assess the value of different stem cells in the process of healing. Increased fibrosis and thicker healed epithelium are some of the side effects of the excessive use of stem cells.

## REFLECTIONS ON THE ROLE OF STEM CELLS IN BURN WOUND HEALING

A lot of controversy can be found in opinion relating to stem cell research. The main argument is that killing embryos will conduct stem cell research, which is unethical. The opposite viewpoint is that even if embryos are used it is not wrong. However, the path that this would lead to i.e. embryo production for research purposes would be wrong. Over time, the public's opinions of stem cell use for therapeutic purposes have become relatively tolerant. The role of enlightening the public regarding the potential that stem cells can reach has proved to be of great benefit. People have become more supportive of stem cell use since they are now aware of their different sources. As far as the acceptance of stem cell usage in burn wound healing goes, a study conducted by Clover showed a positive opinion. A majority of people supported autologous stem cells, and a big percentage was also welcoming using allogeneic stem cells. The percentages were the same between the use of stem cells for burn wound healing or for treating other diseases such as Parkinson's or diabetes.

## CONCLUSIONS

The future of using stem cells for burn wound healing seems very bright. Most of the studies were conducted on animals hence, the application to humans still remains to

done. Therefore, it is crucial that more studies are conducted. In addition to that, the signaling pathways along with stem cells involved in burn wound healing has the potential to be a dynamic and promising research field. ■

## ARTICLE INFORMATION

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