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An update review of stem cell applications in burns and wound care

Lin Huang and Andrew Burd

Department of Surgery, Division of Plastic, Reconstructive and Aesthetic Surgery, The Chinese University of Hong Kong, Hong Kong
Address for correspondence: Prof. Andrew Burd, Chief of Plastic, Reconstructive and Aesthetic Surgery, Department of Surgery, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong. E-mail: kh.ude.khuc.yregrus@drubwerdna

Abstract

The ultimate goal of the treatment of cutaneous burns and wounds is to restore the damaged skin both structurally and functionally to its original state. Recent research advances have shown the great potential of stem cells in improving the rate and quality of wound healing and regenerating the skin and its appendages. Stem cell-based therapeutic strategies offer new prospects in the medical technology for burns and wounds care. This review seeks to give an updated overview of the applications of stem cell therapy in burns and wound management since our previous review of the “stem cell strategies in burns care”.

KEY WORDS: Burns, stem cell, wound

INTRODUCTION

We published a review article in 2007 to give an overview of the up-to-date stem cell applications in burns care based on the published data up to 2006 together with our own clinical experience.[1] This included an introduction to the various sources of stem cells that have been or might be used for burns and wound management; the potential role of stem cells in skin tissue engineering; the wound healing modulation capacity of stem cells especially bone marrow-derived mesenchymal stem cells in treating chronic and non-healing wounds; and the hypothesis of marrow exhaustion or failure following a severe burn injury and the potential of using human umbilical cord blood transfusion for rescue. At the end a diagrammatic overview of the stem cell strategies in modulating wound healing and skin regeneration was proposed, which is reproduced herein with a few modifications as shown in Figure 1.

Stem cell-based therapy is becoming a promising new approach in almost every medical specialty. We should appreciate that in recent years there have been tremendous scientific activity focused on this area of research (basic, preclinical as well as clinical), and rapidly growing evidence is accumulating to support the therapeutic potential of stem cells in skin tissue engineering and cutaneous wound healing.[2] In fact, with the ongoing advances made in the research of stem cell biology, it is likely that more alternative stem cell sources will be described with the potential for various medical applications. Further to the epidermal stem cells (EpSCs) discovered earlier to reside in the interfollicular epidermis, new skin resident stem cells including hair follicle stem cells, neural stem cells, and sweat gland stem cells have been reported and demonstrate the advantages for regenerative medicine in more than just skin regeneration.[3–5] It has been the same with mesenchymal stem cells (MSCs). Adult MSCs have been found to be maintained in almost all post-natal tissues including the umbilical cord and cord blood, dental pulp, and tendon,[6] although bone marrow and adipose tissue are still the main sources that have been most widely evaluated for their medical application potential. A new major breakthrough that has to be mentioned is the successful

development of induced pluripotent stem cells (iPSCs) from mature differentiated somatic cells mostly the skin fibroblasts.[7] iPSCs represent the embryonic stem cell (ESC)-like pluripotent stem cells, which have the ability to differentiate into almost all kinds of cells in our body but circumvent the major limitations of ESC including ethical concerns and potential for immunological rejection. iPS cell technology opens new avenues for the generation of patient-specific pluripotent stem cells, which can be used to establish human disease models for studying disease mechanisms, testing drugs and developing personalized cell therapies.[8,9] With regard to its therapeutic implication in skin, an earlier preclinical study has demonstrated that human ESCs can be differentiated into fully functional keratinocytes and thus can be used to grow epidermis *in vitro* and provide temporary skin substitutes for patients awaiting autologous skin grafts.[10] In a recent study, the feasibility of generating iPSC cells from fibroblasts of patients with recessive dystrophic epidermolysis bullosa (RDEB), an inherited genetic disease characterized with recurrent blistering skin wounds has been demonstrated.[11] Moreover, the RDEB-derived iPSCs were able to generate 3D skin equivalents *in vitro* suggesting that they were fully functional. It seems that iPS cells provides new hopes for curing genetic skin disorder like RDEB because they provide a robust source of pluripotent cells for the derivation of keratinocytes and the transplantation of genetically modified patient-specific iPSC-derived keratinocytes sounds a feasible and straightforward method for cure. However, for burns and wounds of more common types, there is no clear advantage of using ESC or iPSC-derived skin substitutes because generating these stem cell derivatives is a relatively time-consuming, labor-intensive and high cost process.

The main clinical focus of stem cell application in burns and wound care is to target an improved quality of wound healing. With stem cell administration, the medical practitioner would anticipate to achieve earlier wound closure, acceleration in healing, prevention of wound contracture and scar formation, and ideally regeneration of the skin and its appendages. An extended utility of stem cells in burns care also lies in their potential for attenuating the systemic inflammatory response following severe burn injuries and thus may limit infectious complications and result in improved outcomes of the patients.[12] Nevertheless, the remaining challenge of stem cell application for burns and wounds is still to define the optimum source, method of processing and administration from the clinical standpoint, and defining the roles of stem cells in the real clinical situation.[1] We seek to give an illustration of the currently most accessible/realistic clinical applications of stem cells in burns and wound treatment, including a critique on the current clinical use of EpSCs for burn wound coverage, a discussion on the effective way of administration of MSCs to facilitate wound healing and skin appendage regeneration, and the potential use of human umbilical cord-derived stem cells as universal donor cell for temporary wound closure and cord blood transfusion for resuscitation in the acute phase of severe burns patient.

Epidermal/keratinocyte stem cells

The use of cultured epithelial autografts (CEA) for epidermal regeneration in patients suffering from massive burns represents the first therapeutic use of stem cells in burns management. Keratinocytes remain the most easily accessible and successful autologous source for epidermal reconstitution. Epidermal stem cells (EpSCs) are located in both the epidermis and the hair follicle of the skin. Transplantation of CEA containing EpSCs and keratinocytes, either in cell suspension or cell sheet and combined with the use of fibrin matrices to facilitate cell delivery has been a well-established treatment for extensive burn wounds in a number of burn centres around the world.[13,14] In general, this method provides early and efficient wound coverage and shows satisfactory functional result of epithelialization. On the other hand, there have been critical reviews of the hurdles that potentially limit the use of this technique.[14,15] The main adverse factors include the time necessary to culture cells, the reliability of graft ‘take’, the vulnerability to infection, long-term durability, and the cost of the treatment.

Control of infection and proper preparation of the wound bed are of vital importance to a good ‘take’ of CEA. However, to ensure permanent epidermal regeneration, stem cell transplantation is fundamental. Therefore, the effective preservation of the holoclones in keratinocyte culture is required. The holoclones are regarded as EpSC cells that have the greatest proliferative capacity. The reported loss of the cultured autografts after an initial ‘take’ would most probably arise from depletion of stem cells (the holoclones) in culture.[16] Incorrect culture conditions, damage of the exposed basal layer of the cultured epidermal sheet, or use of substrates or culture technologies not pretested for stem cell preservation are considered to be the causes for the loss of epidermal holoclones.[16] Ideally, stem cells in culture should be monitored by clonal analysis described originally by Rheinwald and Green.[17] A careful evaluation of EpSCs preservation in culture is essential for the clinical performance of this life-saving technology.

Various delivery systems have also been developed to improve the clinical applicability of CEA.[14] Keratinocytes have been cultured on biological materials including collagen-based dressing, hyaluronic acid membrane, fibrin matrix, xenogenic (porcine) acellular dermis and amniotic membrane.[14,18] Synthetic polymers have also been developed to facilitate transferring keratinocytes to the wound bed.[14] With new advanced technology in developing temperature-responsive cell culture ware, the preparation of an intact cell sheet can be achieved more easily and simply by reducing temperature without any enzymatic treatments that might damage the cells.[19] Not surprisingly there have been other innovative technologies of cell transfer developed to favor the delivery of CEA sheets.[20]

Currently fibrin glue is an excellent template and has been shown to be an effective delivery substance for cultured keratinocytes. The cell suspension in fibrin glue appears to spread more evenly over the wound surface with no pooling in the inferior aspect of the wound.[21] Keratinocyte sheets cultured on fibrin met retain higher populations of stem cells and have been demonstrated to result in longer and more rigorous graft take.[16,22] Our experience with the clinical performance of autologous keratinocyte spray using fibrin glue demonstrates good clinical results on our burn patients; the cultured keratinocytes are used either alone or in combination with meshed skin autograft for permanent coverage of burn wounds at a later stage. We prepare the wound bed with human cadaver skin or porcine skin. These allogeneic or xenogenic biological dressings are wonderful natural substrates for cell adhesion, growth, and proper differentiation.[14] When used as the cover over the epithelial autograft, they provide not only a temporary dressing, but may also enhance cell paracrine signaling and homing of the cells, thus facilitating a good ‘take’ of the cultured keratinocytes.[23] When CEA is to be used in full-thickness burns, the combined use of a dermal substitute is recommended.[15] When applying CEA to a partial thickness wound where some dermis remains, the bonding between the host and the graft occurs rapidly.[15] The dermis contributes structural elements to anchor the developing basement lamina from the grafted keratinocytes. The use of dermal substitute would compensate for the lack of dermal element in full-thickness wounds. Integra and Alloderm, two commercially produced dermal substitutes have been successfully used in the treatment of major burns.[24,25]

Stem cell therapy may also improve results with CEA or skin autograft. Application of stem cells to a wound bed may prepare the wound with improved neovascularization, augmented local growth factor production and improved wound contracture, thus the graft durability would be enhanced. Several reports on the clinical application of bone marrow MSCs have revealed that grafted MSCs facilitate wound closure with subsequent application of skin autograft in both acute and chronic wounds.[26–28]

The epidermal regeneration obtained with CEA bearing EpSCs can indeed rapidly and permanently cover a large body surface; when undertaken in association with traditional wound care techniques of skin grafting, it can be life-saving for patients suffering from massive full-thickness burns.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs), also referred to as mesenchymal stromal cells, can be isolated from bone marrow and many other sources, such as adipose tissue, umbilical cord and cord blood (which will be discussed later). MSCs are the most promising and substantially evaluated stem cell type for their plasticity in tissue repair and regeneration. MSCs have the capability to differentiate into cells with the mesodermal, ectodermal and endodermal characteristics.[29] They contribute to wound repair and regeneration through direct differentiation or transdifferentiate into tissue-specific cells to reconstitute the tissue; they also release paracrine factors to stimulate the survival and functional recovery of the resident cells.[6] MSCs are found to have immune-regulatory potency in addition to their low immunogenicity feature.[6] Their regulatory capacity enables the modulation of the local microenvironment or niche and the host immune response.[30] As a result, enhanced angiogenesis and suppressed immune response are often observed after MSCs administration. These hold fundamental implications for potential therapeutic applications in burns and wounds.

The clinical application of bone marrow MSCs (BM-MSCs) has been demonstrated in both acute and chronic wounds.[26–28,31] In the treatment of diabetic foot ulcers, the combined therapy with topical application and edge injection of the bone marrow aspirates together with further application of culture-expanded BM-MSCs obtained successful closing and healing of the previously non-healing ulcers.[27] The cultured BM-MSCs delivered using a fibrin spray system to treat acute and chronic wounds was reported in another study.[28] In a recent study, the total nucleated cells (TNC) fractionated from bone marrow were used along with platelets, fibrin glue and collagen matrix to treat diabetic wounds with success.[31] BM-MSC therapy has also been demonstrated with success in both preclinical and clinical settings for treating a particular burn type, the radiation burns.[32,33] With local injection of culture-expanded autologous BM-MSCs, the clinical evolution of radiation-induced complications were significantly improved.[32]

Of note, different means of transplantation of MSC have been described in stem cell therapy. However, the effective method for MSC administration for burns patient has not been well-elucidated. Both local (topical or subcutaneous injection) and systemic applications have been used in the clinical setting. With respect to the local application, the concomitant use of acellular matrices or scaffolds is shown to increase cell homing, differentiation, mobilization and adhesion.[34] However, there is still not enough evidence in terms of analyzing systemic and local effects of stem cell delivery in burns patients regarding different possible routes of administration.[35] We still do not know exactly which percentage of stem cells exerts effects on tissue repair, inflammatory and other systemic responses, respectively, and which route has better advantages (if any) for these respective effects.

In terms of the anticipated routine clinical application, the use of non-fractionated, non-expanded stem cell sources is likely to be more attractive and offer significant advantages. Without subjecting the stem cells to additional extraction or culture expansion procedures, the application is more time-saving and contamination-avoiding. Moreover, using a heterogeneous population containing a rich source of various progenitor cells in addition to MSCs, and their associated growth factors, the application would have added values to the use of culture-expanded MSCs alone. Bone marrow contains hematopoietic stem cells and non-hematopoietic stem cells; it releases a variety of angiogenic, antiapoptotic and mitogenic factors, which are all important mediators in wound healing.[6] We have had positive experience of using topical applications of non-processed autologous bone marrow aspirates on non-healing chronic wounds. We have also applied autologous bone marrow aspirates to chronic unhealed burn wounds and slow-healing donor site wounds and observed a dramatic healing response.

In recent years a significant progress with the plasticity of MSCs in skin regeneration is the demonstration of its potential to regenerate the sweat gland. Human BM-MSCs co-cultured with heat-shocked sweat gland cells (SGCs) exhibited a phenotype conversion from MSC to SGC; the ERK (extracellular signal-

regulated kinase) pathway was found to play an important role in the differentiation.[36] Most importantly, when these pre-differentiated BM-MSCs were transplanted into fresh skin wounds after excision of anhydrotic scars resulting from deep burn injury, the perspiration function of all transplanted areas was found re-established in 2-12 months' time, indicating the regeneration of functional sweat glands.[37] Further development with an epidermal growth factor (EGF) microspheres-based engineered skin model to deliver the BM-MSCs was found more favorable to the healing quality and sweat gland repair in an animal model.[38] In full-thickness burns, sweat gland can not be regenerated by healing. The success in regenerating functional sweat gland from MSC transplantation would provide a significant benefit for patients surviving extensive deep burns.

Another exciting area is that in analogy to BM-MSCs researchers have found the potential of adipose-derived stem cells (ADSCs) to be applied in skin regeneration strategies. ADSCs can be isolated from liposuction aspirates which are more easily obtainable in adequate quantities with little patient discomfort as compared to bone marrow procurement. Through extensive washing, removal of the red blood cells and enzymatic break-down of the extracellular matrix, the resultant cells are known as stromal vascular fraction (SVF) [Figure 2]. SVF is a heterogenerous mixture containing adult MSCs and also endothelial cells, preadipocytes, fibroblasts, leucocytes and hematopoietic stem cells.[39] The MSC population can be further isolated by their ability to adhere to plastic ware and expanded in culture. The SVF has been studied as a supplement to free fat transfer in soft tissue augmentation to increase yield.[40,41] The applicability of ADSCs for wound repair and regeneration has been demonstrated in a number of experimental models both *in vitro* and *in vivo*.[42–44] In our unit we are looking at the SVF and using it to enhance the revascularization of fat grafts used for contour defects in post-burn patients. Our experience indicates that this is another potentially exciting application for stem cells in burns and wounds.

Human umbilical cord/cord blood stem cells

Human umbilical cord and cord blood remain the most abundant, readily available and non-ethically controversial source of stem cells considering the global birth rate of about 133 million a year in 2011.

The cord blood is a rich source of haemopoietic stem cells with naïve immune status for clinical application.[45] Non-haemopoietic stem cells are also found in umbilical cord blood and have been demonstrated to be able to differentiate into epithelial cells under both *in vitro* and *in vivo* condition.[46–48] The cord tissue retains various stem cell types that can be isolated from different layers of the cord including the vessels (the artery and the veins), the gelatinous supporting matrix Wharton's jelly, and the outer lining [Figure 3].[49,50]

The umbilical cord-derived MSCs (UC-MSCs) hold excellent potential in terms of their *in vitro* expansion capacity, multipotency and immune-regulation properties. UC-MSCs have similar immunophenotypic and functional characteristics to the BM-MSC;[51,52] they are also capable of differentiating towards mesoderm-derived mesenchymal tissues such as bone, fat and cartilage as well as a growing number of endodermal or ectodermal cell lineages.[53,54] In this regard, they hold the same promise as BM-MSCs in tissue repair and regeneration.

Another current interest is the umbilical cord lining, which offers a source of epithelial stem cells. The umbilical cord lining membrane resembles a structure of the early fetal epidermis; and the cord lining epithelial cells (CLECs) share the common features of epidermal keratinocytes in their expression pattern of cytokeratins and cell surface markers, and their response to differentiation stimuli.[55,56] We and others have demonstrated the epidermal and pluripotent stem cell characteristics of CLECs and the differentiation potential of CLECs towards epidermal reconstitution in both *in vitro* and *in vivo* models.[50,57] CLECs have also been shown to hold the promise for corneal epithelial regeneration,[58] All these

would open up the potential clinical application of these cells for epidermal/epithelial reconstitution in wound healing. These cells have a low immunogenicity.[50] This suggests that they may serve as a universal donor epithelial cell source. Human epidermis serves as a protective covering against loss of endogenous fluids and invasion of exogenous microbial. Delayed wound closure in burns would worsen the patient's susceptibility to infection and increase the incidence of scarring and even mortality. Timely application of CLECs as epithelial allograft may offer an alternative to burn wound closure leading to improved mortality, morbidity and the overall quality of scarring. This truly would have a dramatic impact on burns and wound care if the real potential of such an approach could be validated in clinical studies. There have been ongoing clinical trials to use these cells for burn resurfacing as well as treating chronic diabetic wounds.[45] We are going to conduct a clinical study to evaluate the application of a biological dressing composed of cultured epithelium of human umbilical cord derived epithelial cells seeded on a fibrin matrix in the healing of recurrent wounds in a RDEB patient. We hope our experience with such an approach in this specific skin condition would open up more broad clinical application potential of these cells for burns and wound management.

Another promising field in the acute care of the severe burns patient is the use of allogenic stem cell-enriched sources, i.e. human umbilical cord blood (HUCB), to meet acute response demand whilst protecting the autogenic stem cell bank, the bone marrow[1] . Immediately after burn injuries, MSCs multiply in the bone marrow and migrate to the injury sites contributing to the wound healing and tissue repair.[12] Hematopoietic and endothelial progenitor cells also mobilize from the bone marrow to the wound contributing to the inflammatory response, autolysis and neovascularization.[12] A study looked at the extend of influence of thermal injury in the number of circulating mononuclear cells (MNC) including endothelial progenitor cells (EPCs) in burns patients and found significant negative correlation with the fatal outcome of the cases.[59] In severe burn trauma, the systemic inflammatory response may lead to sepsis and multiorgan dysfunction; bone marrow suppression has been described.[12] Stem cell therapy may offer an alternative to large-volume resuscitation in severe burns.[12] When considering HUCB as an adjunct therapy for a critically ill patient, it would be more appropriate to regard it as a transfusion rather than a transplantation. Our experience of this has been limited by our local regulatory authorities who regard HUCB transfusions as being transplants and require timely and costly HLA typing. There has been sufficient published evidence to indicate both the safety and efficacy of HUCB transfusions/infusions in a range of clinical conditions.[60–62] With respect to the medical implication of HUCB transfusions/infusions in burns we would like to explore this further in the context of a prospective multicentered clinical trial in the near future.

SUMMARY

Stem cell-based therapy has offered a novel and powerful strategy in almost every medical specialty including burns and wound management. Stem cells have proven to have tremendous potential in enhancing wound healing and facilitating skin regeneration. The choice of suitable stem cell sources in sufficient quantity, adequate culture conditions to preserve stem cell property, appropriate matrices or scaffolds to improve cell delivery efficiency will all have a great impact on the clinical outcomes of stem cell application. In terms of the anticipated clinical practice, stem cell therapy has to be improved to the point that hospital can put safe, efficient, and reliable protocols into practice. These will eventually advance the standards of burns and wound care.

Footnotes

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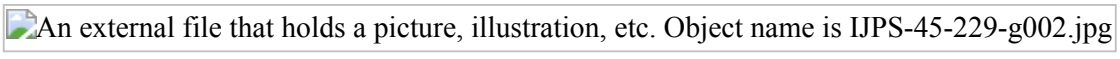
Figures and Tables

Figure 1

Stem cell strategies in burns and wounds" modified from Figure 7 [I]

Figure 2



Adipose tissue-derived stromal vascular fraction (SVF)

Figure 3

Human umbilical cord compartments and stem cells within
