Int J Burn Trauma 2019;9(1):1-12
www.IJBT.org /ISSN:2160-2026/IJBT0087087

Review Article

The effects of stem cells on burn wounds: a review

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Received October 21, 2018; Accepted November 12, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: Introduction: Stem cell therapy application is at the vanguard of regenerative medicine across all medical disciplines. Stem cells are of special interest in burn wounds, as they have multiple potential indications for application; including - accelerating wound healing, improving skin regeneration to incorporate skin appendages, reducing fibrosis and improving scarring. Methods: A literature review was performed using both MeSH and keyword searches of PubMed to identify all potentially suitable publications. Search criteria were restricted to the English language, but acceptable English translations were sought for inclusion. Inclusion dates were from 2003 up until and including 2017. Studies included looked at stem cells in burn wounds only. Results: There were 692 potentially suitable publications of which 72 were included for review. These included a systematic reviews and original research articles. Conclusions: Stem cells accelerate burn wound healing by inducing neo-angiogenesis, collagen deposition and granulation tissue formation. They modulate the inflammatory response and reduce the risk of infection. They can regenerate skin appendages and halt he zone of stasis in acute burn injury. However with these pre-clinical animal model studies we must be cautious with our interpretation of this novel therapy.

Keywords: Burns, wounds, stem cells, regenerative medicine, tissue engineering

Background

Stem cell therapy application is at the vanguard of regenerative medicine across all medicinal disciplines. There have been a multitude of studies published to date with promising results of their efficacy, particularly in the fields of tissue transplantation and medical oncology. Stem cells themselves are a hetergenous group of cells that can be naturally procured from embryos or adults or via artificially means by manipulating the differentiation of pluripotent stem cells, which is becoming more predictable [1].

Stem cells are of special interest in burn wounds, as different stem cells can be effective on different wound beds [2-4]. Burn injuries create multiple indications for potential stem cell applications including - expediting wound healing, improve skin regeneration to incorporate skin appendages and reducing fibrosis to improve scarring. However preclinical studies still demonstrate concerns especially regarding cell differentiation, cell fusion and signaling with growth factors, which are delaying its transition into mainstream therapy [5].

At present patients with a significant burn injury are being treated using traditional debridement and grafting with or without the use of skin substitutes, allograft or cultured epithelial auto-grafts.

However surgeons are collaborating more than ever aiming to incorporate stem cells as a more efficacious treatment option to the current surgical management paradigm. This will be hopefully be implemented with low risk, low morbidity and with added benefits over conventional treatment such as regenerated skin appendages, minimal hypertrophic scarring and a reduced inflammatory response [1-3].

Methods

A Pubmed search was utilized to identify available literature up to and including 2017 (**Figure 1**). The topic of “stem cells” and “burn wound healing” were explored to identify any conceptual significant issues. Subsequent to this, a search strategy was devised using several key terms; “adipose derived stem cells”, “mesenchymal stem cells” and “burn wounds” “healing”. Employing these key search criteria a bib-

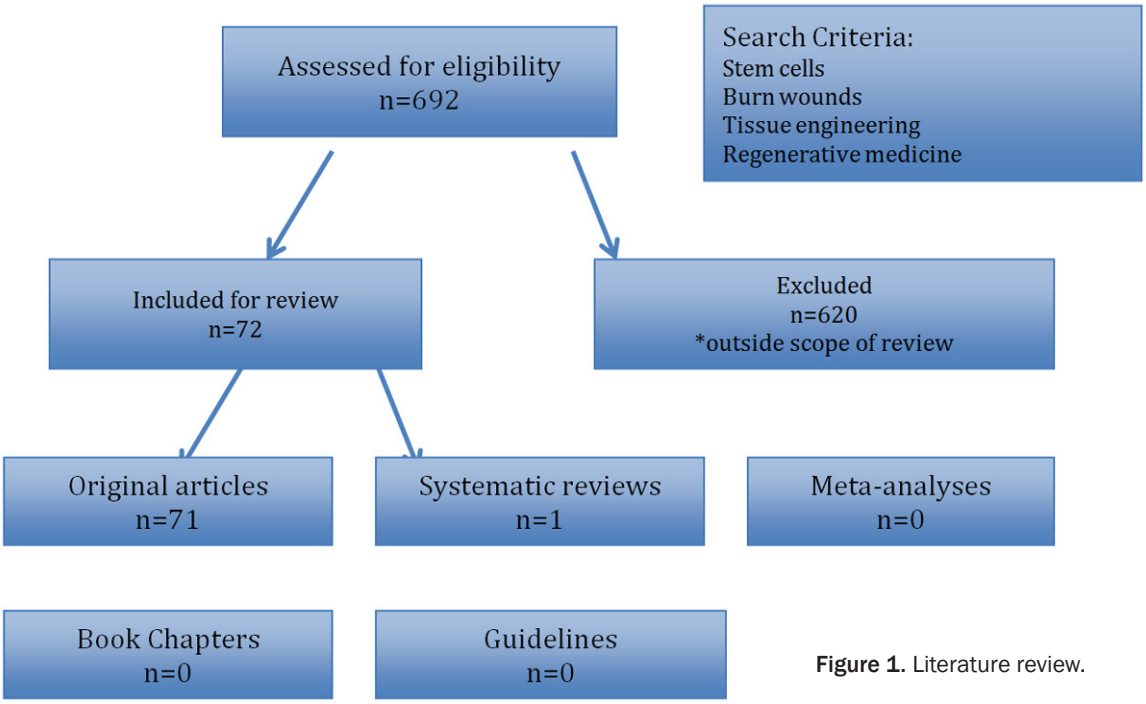

Figure 1. Literature review.

liographic search was performed on pubmed only. Additional search criteria included "regenerative medicine" and "tissue engineering".

Search criteria were restricted to the English language, but acceptable English translations were sought for inclusion. Inclusion dates were from 2003 up until and including 2017.

Studies included looked at stem cells in burn wounds only. Studies were excluded from this review were those looking at chronic wounds, diabetic wounds, corneal burns, general wounds and those looking at role of stem cells in scarring only.

A staged review of article titles and abstracts was conducted to identify and subsequently select all articles that correlated with the inclusion criteria. Original articles (observational, cohort, cross-sectional, case-control, longitudinal and experimental), systematic reviews, and meta-analyses were all included for review.

Additional studies were found after reviewing the related citations and references of the included papers.

Stem cells

Classification

Stem cells are classified by their origin as either embryonic or adult stem cells according to the developmental stage. Embryonic stem cells are derived from the blastocyst [7, 8]. They are propagated at six to nine week's gestation at the primitive gonadal ridges [9].

Stem cells may be pluri, multi- or unipotent [2]. The mammalian zygote is unique in that it can create any cell or tissue or any organism making it totipotent [10]. The pluripotent cells generate cells/tissues from either ecto-, meso- or endoderm layers [11], the multi-potent cell can generate more than one cell lineage confined within a group of related cells and unipotent cells create a single cell type [12].

These cells can remain undifferentiated and plastic referring to their ability to change into an alternative tissue type [13]. In vivo they have a low turnover but may replicate rapidly to aid tissue regeneration and wound healing [14].

Sources

Embryonic stem cells (ESC's): Embryonic stem cells (ESC's) originate from the blastocyst of an embryo or in an in-vitro state in with an extracellular stimulus. They produce all three germ layers [15]. Human embryonic stem cell use is limited and controversial as it requires terminating the embryo [16], hence the majority of research is carried out using adult stem cells (ASC's) [17, 18].

These cells undergo unlimited replication invitro, which allows expansion into undifferentiated groups to safeguard the phenotype permanently [19].

Umbilical cord stem cells (USC's): Human umbilical cord stem cells are the best source of stem cells [20]. They have endothelial progenitor cells, in addition to haematopoietic and non-haematopietc stem cells [21, 22]. The cord is composed of various layers including the cord vessels, the whartons matrix, the amniotic membrane and the subamnion [20]. Each provides stem cells, with the matrix providing a potential yield of a billion MSC's in 30 days [10].

These umbilical MSC's can be transformed into skin, endothelium or bone [23].

Mesenchymal stem cells (MSC's): Mesenchymal stem cells are predominantly harvested in adults from bone and adipose tissue [24, 25]. They also may be sourced from the umbilical cord [26], a tendon [27], and the placenta [28]. Their use is halted due to two main factors- ethics and tumorgenicity [15].

They are defined by their ability to change into different cell lineages such as cartilage, bone and fat, and express cell markers such as CD 36 [29, 30]. The CD 36 antigen distinguishes between ADSC and BMSC's [14, 31].

They modulate the immune response via release of growth factor and cytokines [32]. They are pro-angiogenic, anti-apoptotic and anti-fibrotic to the local cell [33, 34]. This combination of effects stimulates local cell populations in the target organ-e.g skin to self-repair [35].

Bone marrow derived stem cells (BMSC's): Bone marrow derived stem cells were traditionally the main source of adult mesenchymal stem cells, however their harvest was invasive with low yields [20, 36]. They have the ability of "cell fusion", which is involved in tissue regeneration and immunity [37, 38]. They can be cultured and utilized in wound management however data is equivocal on the results to data [39].

Adipose tissue-derived stem cells (ASC's): Adipose tissue-derived stem cells have been widely discussed across the plastic surgery literature [40].

They are a heterogeneous group, differentiated by the type of adipose tissue from which they are harvested [41]. White adipose tissue typically stores trigycerols and brown produces body heat. Brown adipose tissue is commonly found in the neck, mediastinum, supraclavicular and parascapular regions. White is located in the visceral and subcutaneous planes.

Baglioni et al demonstrated that abdominal subcutaneous ASCs have increased adipogenic potential and faster growth rates versus their visceral fat counterparts [35]. Evolving data suggests that ADSCs are pluripotent and capable of differentiating into all three germ layers [42].

The aspirated processed fat contains a milieu of cells such as fibroblasts, macrophages, endothelial and stem cells [4]. These stem cells can be cultured to up to a 1000 times their yield making them distinctly more attractive than BMSCs [44]. In addition adipose tissues produce hormones such as leptin, which help in wound regeneration [4, 44]. All these influences promote regeneration through immunomodulation, neo-angiogenesis and endogenous repair mechanisms [35, 45].

These ASC's stem cells are really the "holy-grail" in regenerative medicine as they are widely available, easily obtainable and propagated, have pluripotent potential and promote wound healing [46].

The effects of stem cells on neo-angiogenesis and immune response

The first reported application of stem cell therapy in burn care was by Shumakov et al in 2003 [47]. They compared the effects of mesenchymal bone marrow derived stem cells (BMSC) to embryonic fibroblasts in burn wounds [47]. In an animal model study with 40 rats, they showed that transplantation of allogenic and autogenic fibroblast like BMSC, expedited wound healing by promoting neo-angiogenesis and reducing inflammation. Study rats treated with autogenic stem cells demonstrated a dramatic decrease in burn surface area [47]. They postulated regeneration was due to the stem cells low differentiation [47].

Rasulov et al reported a human study involving BMSC's [48], utilizing topically applied allogenic fibroblast like mesenchymal stem cells in a

female patient with 40% total body surface area burns. They noted faster neo-angiogenesis, wound healing and rehabilitation. He too demonstrated in animal studies that fetal like MSC's harvested from the rats themselves and then applied to their burn wound beds expedited healing via decreasing cellular infiltration and increasing local neo-angiogenesis [49]. This created an environment more conducive to earlier wound healing [49].

Ha et al compared effects of stem cells on wound healing in partial thickness burns [50]. He transfected BMSC's with adenovirus as a vector with hepatocyte growth factor. Rats were then randomized into four groups, with the therapeutic group labeled as AD-HGF-modified MSC's. This group had more significant re-epidermal growth at a shorter interval, less type 1 collagen and a thicker epidermis [50]. These effects were realized through the cytokine activity and modulation of stem cell differentiation [50].

Xue et al intra-dermally injected mice with human obtained BMSC's at their burn wounds versus a control. Burns treated with stem cells healed far superiorly and with a more profound neo-angiogenesis effect, and these mice regained body weight faster with no corresponding tumour growth [51].

Liu et al used human umbilical cord MSCs (hUC-MSCs) on burns in rats and found in comparison to placebo, that intravenous injection of stem cells labeled with GFP fastened wound healing. They decreased inflammatory cell infiltrate, levels of Interleukin-1 and 6, TNF alpha, and the ratio of collagen types I/III were higher in the therapeutic group [52]. The laser flow Doppler confirmed markedly higher neo-angiogenesis in the stem cell versus control group [52].

In 2014 Atalay et al looked at the stromal vascular fraction (SVF) and its effect on partial thickness burns [53]. The SVF is an autologous mixture of pre-adipocytes, MSC's, endothelial cells, B and T cells and macrophages. Rat adipose tissue was harvested from the groin and processed to separate out the SVF. Rats were scalded producing deep partial thickness burns and divided into groups. One of which received the SVF via intradermal injection. Histologic analysis revealed higher VEGF levels, reduced inflammation, increased fibroblastic activity and accelerated neo-vascularization with improved wound healing in the SVF group [53].

In 2015 Zhang et al looked at the effects of human amniotic epithelial stem cells derived exosomes (UC-MSC) in cutaneous wound healing [54]. Amniotic tissue was harvested from pregnant women. Isolated epithelial stem cells from the amnion were then cultured in a bovine derived serum. Full thickness defects were created in rat dermis and different concentrations of the exosome were injected versus a saline solution.

Wound healing was standardly assessed at days 7, 14 and 21 [54]. The human amnion epithelial exosome groups all had similar rates of healing, but were much more advanced than the control group. An increased rate of re-epithelialization, expression of CK-19 and collagen production was noted. In addition the AKT pathway was activated by the exosome reducing apoptosis secondary to thermal stress [54].

Loder et al [55] induced a 30% TBSA burn in a rodent and used ADSCs from adipose tissue to examine their effect son four subgroups. The first was the processed adipose tissue, then ACS's alone, mixed adipose and ASC's and lastly saline. Therapeutic groups demonstrated improved healing in relation to burn depth, apoptosis rates and surface area. However there was no significant increase between them and placebo group in epidermal proliferation or revascularization at five days [55].

Karimi et al [56] created full thickness burns in mice with similar % TBSA and grouped them into three-ASC's, adipose group and control. The wound surface area and burn eschar thickness were smaller in the ASC group, but no significant differences were noted in any group. Collagen synthesis was more aberrant in the ASC group but again no differences existed between each group [56].

Clover et al in 2015 looked at allogeneic MSC's, but specifically culture modified monocytes, to improve burn wound healing in a porcine model with contact burns [57]. This group assessed two cell sources, allogeneic MSC's and autologous culture modified monocytes on burn wound healing. Cells were administered with a fibrin matrix and results demonstrated MSC's

statistically reduced burn wound size, increased collagen and epidermal regeneration versus monocyte group after a single application [57].

Caliari-Oliverira et al looked at xenogenic MSC's to improve wound healing and modulate the immune response in an extensive burn [58]. They chose to use xenogenic stem cells to avoid the need and delays in time propagating an autologous cell line. MSC's were harvested from mice bone marrow, expanded in-vitro and injected intra-dermally to the wound edge.

MSC treated rats had a significant longer survival and at 60 days post burn, demonstrated higher % surface area healing [58]. Immune effects were seen in the form of altered CD4 and in T cells in the spleen and skin [58]. Plasma cytokine levels such as TGF-beta, IL-10 and IL-6 were altered in the MSC group versus control [58].

Zhang et al exmained the effects of MSCs on burns in 2015 [25]. Human MCS's were harvested from umbilical cords, cultured and transplanted into burned rat groups subcutaneoulsy. Serial blood sampling was performed and WBC, CRP, IFN-γ, TNF-α, IL-6 and 10 were detected. In the MSC group all inflammatory markers were slightly increased versus the controls. The stem cell group exhibited a faster healing rate than the control [59].

In 2016 Biley et al reiterated previous literature reports of ASC's [60]. Full thickness burn wounds on the spinal region of mice induced and injected with either ASC's or a placebo. Time to healing was assessed to day 21 and a molecular investigation to study the effects of the ASCs was used. There was increased vascularity in wounds by day four and enhanced adipogenesis and increased collagen III to I deposition raton on mRNA in the stem cell group [60].

The most recent paper addressing stem cells in burn wounds was by Muhammad et al [61]. This focused on acid burns that were treated with transplanted ASC's. They had accelerated wound healing and found pre-conditioning the ASC's with ascorbic acid was advantageous to healing [61]. In the study multimodal imaging using a functional MRI assessed ASC survival. They found that, while the lifespan of ASC's is short, they still not only healed wounds faster but also reduced hair follicle loss [61].

The effects of stem cells on radiation therapy induced burns

In 2004 Chunmeng et al found that irradiated rats treated with systemic transplantation of dermis derived pluripotent stem cells (DMC's) healed faster than those without. The effects seen were due to the stem cells producing epidermal cells, fibroblasts and cytokines such as VEGF and PDGF [62].

Latalide et al [63, 64] looked at burn wounds induced by radiation therapy. Mesenchymal stem cells were shown to reduce inflammation and improve wound healing [63, 64]. Building upon the application of stem cells in irradiated human cutaneous burns, Zong et al, modulated stem cell application with human beta defensin 2 [65, 66]. This was performed using adenovirus as vector.

These modified stem cells illustrated antibacterial properties advantageous in infected burn wound healing [65, 66]. The transplanted stem cell therapeutic group also demonstrated a faster rate to complete healing. This looked specifically at the microorganism pseudomonas aeruginosa, which is a commonly seen pathogen in burns patients [65, 66].

Agay et al examined irradiated wounds in pigs and examined the effects of intradermal injection of mesenchymal stem cells on local wound healing in the context of Cutaneous Radiation Syndrome (CRS). The pathophysiology of the burn wounds was similar to that of humans. They reported an accumulation of lymphocytes within the wound bed at the dermal junction in the pigs treated with bone marrow derived MSC's and improved vascularization versus their control group [67]. This study was novel in that in was highly similar to a human model allowing formulation of a treatment strategy.

Riccobono et al used adipose derived stem cells of three variant forms - autologous, allogenic and acellular on burn wounds. Unsurprisingly only the autologous group demonstrated superior wound healing with a reduction in pain and no necrosis [68]. Another porcine model, took BMCS's and combined them with skin derived keratinocytes [69]. This was to examine the efficacy of a cultured cutaneous substitute (CCS) to expedite healing in an irradiated field. Both groups were crossed with a

recombinant retrovirus to inoculate human (h) platelet derived growth factor A.

The CCS were created by adding BMCS's from pigs to amniotic membrane obtained from humans with skin keratinocytes or with modified human "h" platelet growth factor A. The CCS with bone marrow stem cells and keratinocytes transplanted healed the wound faster with improved epithelialization, granulation and angiogenesis versus controls [69]. Increased amounts collagen deposition were found in this group too [69].

Xia et al [70] took human beta defensin 3 with human VEGF 165 and transfected BMDS's cells to treat burns. The supernatant of the stem cell group induced endothelial cells to multiple and migrate to the wound site. They inhibited pathogen growth such as fungi and bacteria [70]. They were injected topically at the irradiated wound and induced a shorter interval to healing. There were improved levels of granulation tissue and collagen deposition with corresponding cutaneous adenexal regeneration [70].

Motamed et al again looked at seeding skin substitutes with stem cells, he used amniotic membrane combined with ASC's or fetal fibroblasts to assess regeneration of burn tissue in rats [71]. Full thickness burns were created and subsquently excised and randomly covered with Vaseline gauze (control), human amniotic membrane (HAM), human fetal fibroblasts seeded on HAM (HAM-FF), or human adipose-derived stem cells seeded on HAM (HAM-ASC), and followed by wound closure and histological assessments [71].

Early wound closure rates at day seven and 14 were highest in the HAM-ASC group and this group had the lowest inflammatory cell infiltrate in conjunction with the HAS-FF group. They concluded that this cell based tissue engineered dermal substitute model offered accelerated wound healing [71].

The effects of stem cells when used with an acellular dermal matrix (ADM) and/or expander/culture medium

Adult BMSC's were applied topically to collagen scaffolds and then applied to iatrogenically induced deep dermal burn wounds in pigs by Liu et al [72]. This intervention resulted in improved vascularization and keratinization in the healed wound with noted less dermal contraction.

Kinoshita et al used fibroblast growth factor with and without expanders in burn wounds in 35 pigs [73]. The combination of expander with basic fibroblast growth factor produced accelerated neo-angiogenesis and more epidermis and dermis versus expander alone. Further studies of these results using electron microscopy illustrated the combination model had more robust cutaneous adenexal structures with an intact epidermis and dermis. This confirmed basic fibroblastic growth factor as an agent that can both induce and maintain healing after acute radiation exposure to soft tissue [73, 74].

Mansilla et al used an ADM product in combination with anti-CD44 antibodies to encourage the attachment of stem cells to promote improved burn wound healing in a porcine model [75]. This was achieved by using ADM's in combination with biodegradable nanofibres coated with growth factors. These integrate with the wound biologically and amalgamate to create a scaffold, which simultaneously attracts and anchors circulating growth factors [75]. This improves cutaneous burn healing but also skin appendages such as hair follicles [75]. It may too have applications in cosmetic procedures in the future [75].

Another study examined uncultured ASC's seeded onto a collagen scaffold to improve dermal regeneration, enhancing angiogenesis and structural changes post thermal injury [76]. Uncultured ASC's were applied to a collagen-based matrix to assess if they would enhance healing of the graft [76]. Full thickness burns were created in mice, excised after 48 hours and groups were randomized to ASC's or a control. Analysis showed accelerated maturation of the wound, increased collagen deposition and decreased wound bed depth in the stem cell group [76]. There was increased neovascularization and luminal cross sectional area and vessel maturity at day 14 and 21 in the ASC seeded matrix group [76].

Guo et al [77] seeded MSC's to small intestine submucosa (SIS) to repair partial thickness burns in rodents. A scald burn was induced and

at day three the seeded grafts were implanted onto the burn area. They compared SIS independently to MSC seeded SIS, and found that the MSC group accelerated granulation formation, angiogenesis, healing and induced proliferation of neo-epidermal cells [77].

In 2017 Chen et al [78], examined the effects of ASC's differentiated adipocytes on burn healing in rodents. Partial thickness burns were induced to the mice who were divided into five subgroups. There was a control; ASCs; differentiated adipocytes, -ibmx (3-isobutyl-1-methylxanthine)+insulin and +ibmx[d1-5]+insulin) subcutaneously and the fat was prepared by the coleman technique [78].

Adipogenic differentiated ASCs exhibited equivalent healing potential to ASC and fat injections, but differentiated adipocytes (+ibmx[d1-5]+insulin) and fat transfer propelled early healing relative to ASC [78]. There was reduced inflammation and fibrosis in the superficial dermal layer in the +ibmx(d1-5)+insulin and fat injection groups, while those reactions were mild to moderate in ASC group [28]. Differentiated adipocytes had comparable healing rates to ASC and fat injections, but differentiated adipocytes (+ibmx[d1-5]+insulin) and fat transfer expedited healing in comparison to ASC [78].

The effects of stem cells on acute burn injury

While studies to date have all looked at accelerating wound healing in animal models predominantly, Singer et al looked at whether stem cells in the acute burn setting could halt progression of the burn [79].

This is response to the fact that burns are a dynamic injury, which may progress unlike a mechanical trauma. He used a rat model with a control group where one received MSC's via their tail versus a saline injection in the same location exactly one hour post injury. The model was to examine the unburned spaces between the iatrogenically induced burn sites, which were symmetrical in each group by day seven.

Theses spaces were representative of the zone of ischemia peripheral to zone of direct contact "necrotic zone". The results showed that only 20% of the stem cell group had necrosis in between the burns in comparison to a 100% of the control group [79]. Stem cells are now trying to be combined with dressings for burns, and Yang et al attempted to mix them using a fibrin glue and applying them topically to 30 rats which sustained scald burns [80].

He controlled the study with three groups, stem cells and glue, glue alone and no intervention. The stem cells used were allogeneic BMDSC's. Each rodent had two burn injuries on their back and after 30 days of therapy groups were evaluated. The study group demonstrated accelerated burn healing with skin appendages visible, which did not feature in either of the other groups [80]. They felt this therapy of clinical importance for emergency burn surgery and/or skin grafting procedures [80].

In 2013 Oksuz et al [81] looked to see of they could alter the zone of stasis and halt burn progression in an acute burn with subcutaneous injection of MSC's. They administered the MSC, which were harvested from bone marrow of rats 30 minutes after the acute burn injury to the study group and saline to the control group.

After 72 hours a scintographic analysis was performed to assess vital tissue at the zone of stasis. Samples of skin were taken for immunohistochemistry to analyze cytokine and apoptosis levels. While there was no difference in cytokine levels, the study group had statistically significant improvement in tissue survival at the stasis zone [81]. The apoptotic rate was dramatically increased in the control group [81]. They concluded that this intervention has a benefit to salvage the zone of stasis in acute burn injury [81].

The effects of stem cells to incorporate skin appendages

Blum et el study harvested epithelial stem cells from mice and injected them locally to burned skin [82]. They assessed a G-protein related receptor called LGR6+ (leucine-rich repeat-containing G-protein coupled receptor 6) isolated from the adnexal elements of the epithelial stem cells, namely the bulge of the hair follicle.

This was to assess their ability to regenerate a wound in which there is complete loss of the epidermis/dermis.

They identified increased epidermal and PDGF/VEGF in the stem cell group [82]. This group too produced hair follicles and had increased neovascularization in the wound [82].

A review of cell-based therapies in burn wound as a therapeutic option was performed in 2014 [83]. This review by Gardien et al illustrated breakthroughs and reassurances in our current understanding of epidermal and MSC's combinations for skin and skin appendage regeneration [83].

A novel effect of stem cell in burn wounds is to regenerate sweat glands, unlike dermal regeneration where significant progress has been made, this field in still in a primitive stages. Ma et al built upon the work of Zhang et al [84] in this arena. They examined the ERK, EDA-A1 and NF-kB signaling pathways and concluded regeneration of sweat glands can be performed by two methods, namely proliferation and differentiation of sweat gland stem cells in situ [85] and reconstruction of sweat glands by transplanting SGL stem cells [86].

This evolving field offers the new hope for sweat gland regeneration after a severe burn [87].

The challenges using stem cells on burn wounds

There are several challenges to the use of stem cells on burn wounds, the predominant one being the effective application of them to the burn wound. They can be administered topically, intravenously or in conjunction with an ADM but no ideal method has been identified. Unfortunately we still cannot accurately identify the percentage of cells that act locally on wound healing versus those that enter the circulation to produce the systemic effects reported in our discussion. Research into this challenge is ongoing in the form of stem cell tracking in vivo via gene imaging and PET scans to detect stem cell location post transplant [88].

Other challenges that exist are undoubtedly legislation and biosafety. Stem cell therapy and tissue engineering are considered 'advanced therapy products' (ATPs). The U.S. Food and Drug Administration states cell therapy is the provision of autologous, allogeneic or xenogeneic non-germ cells, which have been manipulated, processed, propagated, expanded, selected ex vivo, or drug-treated [89].

These should be considered like drugs and demonstrate preclinical safety and efficacy. There should be no risk for donors of transmission of infectious and/or genetic diseases and no risk for recipients of contamination [90].

Important clinical aspects like dose characteristics, risk stratification, pharmacovigilance and traceability issues must too be strictly regulated [90].

Conclusion

Stem cells accelerate wound healing via a complex series of pathways that seek to promote neo-angiogenesis, collagen deposition and granulation tissue formation. They alter our immune response by decreasing the severity of the inflammatory cascade. This may decrease the risk of infection. Stem cells are key in regeneration of cutaneous appendages such as hair follicles, sweat and sebaceous glands, which would improve aesthetic outcomes for patients.

As the majority of the research work to date has been performed in pre-clinical animal model studies we must be cautious with this novel therapy. We must look to the future and establish safe, ethical and ideally randomized clinical trials, to assess them formally in a human model.

Acknowledgements

We provide consent for publication of this article.

Disclosure of conflict of interest

None.

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