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Mesenchymal Stem Cell Therapy for Burn Injury: Literature Review

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Abstract: ***Stem cell therapy has been considered as the final frontier therapy to treat various disease including wound that caused by burn injury. Despite its systemic effect, severe burns raise a great challenge to gain a good wound healing process. Using stem cells in promoting burn wound healing gives some advantages such as they can enhance the healing process of the burn wounds and decrease the inflammation process with minimum scar progression and fibrosis. Mesenchymal stem cells (MSCs) are commonly used to treat burn wound due to their features to be able to differentiate into cells within the mesodermal, ectodermal and endodermal lineage and are abundantly available in human tissue.This review article gives an insight about physiology of burn wound and skin regeneration, characteristic and source of MSCs as well as the use of MSCs as skin wound therapy.***

Keywords: burn injury, skin regeneration, mesenchymal stem cell, therapy

1. Introduction

Burn injuryinvolves an area of tissue damage that caused by the effects of heat directly from the transfer of thermal energyorindirectly when some other form of energy is converted into thermal energy [1]. It is one of the most serious trauma case especially in low and middle income country where over 95% of all burn death occur [2].Skin is the largest organ in human body that has protective, perceptive and regulatory functions. Extreme loss of skin that is caused by injury and illness will result in substantial physiological imbalance and may ultimately lead to disability and mortality [3]. Despite its systemic functional consequences, major burn patients also have skin coverage problem results in devastating effect cosmetically [4].

The best approach for replacing the lost skin is with the skin itself. To achieve a success skin grafting requires adequate wound bed preparation, careful selection of suitable donor site and appropriate post-operative wound care. Some problems could arise during the early postoperative period such as: the formation of blisters due to the absence of the Basement Membrane Zone (BMZ) that provides connection between the new epithelial layer, the inclusion cyst development caused by the secretions from the adnexal structure beneath the skin graft, sponge deformity, infection and malignant degeneration/Marjolin ulcers. The replacement of epidermis alone using cultured epithelial autografts (CEA) also remains a challenge due to theirfragility because of the dermal component lacking [5].

Stem cells therapy has been considered to be an alternative and effective approach especially for severe burn cases. The advantages of using these cells in promoting burn wound healing are they can enhance the healing process of the burn wounds and decrease the inflammation process with minimum scar progression and fibrosis [4,6,7].However, many questions and challenges are still persist to perform this therapy such as: the most effective delivery techniques of these cells, the most optimum sources for wound healing and the long-term effect of MSCs therapy in burn injury.

2. Physiology of Burn Wound and Skin Regeneration

Burn Wound Healing

There are three zones of burn wound including coagulation zone, stasis zone and hyperemic zone. The region of coagulation in the central represents the most damaged tissue at the time of injury because the cells in this area are coagulated and necrotic. This is surrounded by a zone of stasis which characterized by vasoconstriction and ischemia. Outside the zone of stasis is a zone of hyperemia, where microvascular perfusion is not impaired and vasodilatation occurs due to the release of inflammatory mediators from resident cutaneous cells. The area of stasis can convert to necrotic tissue within the first 48 hours following thermal injury as the results from prolonged decreased perfusion and development of edema and infection [5,8].

The healing process of the burn wound depends on the depth of the wound itself. Based on its depth, burn wound can be classified as follows: 1) first-degree burns or epithelial burns where the skin is only erythematic without blister formation, 2) second-degree burns involving epidermis and dermis at the different thickness, it can be divided as second-degree superficial that only affect papillary dermis where vesication and inflammation is shown and second-degree deep that involves deep reticular dermis results in eschar formation, 3) third-degree burn or full thickness burn, the characteristic of this degree wound is often dry, leathery, black/white, painless and eschar formation is seen [5,9].

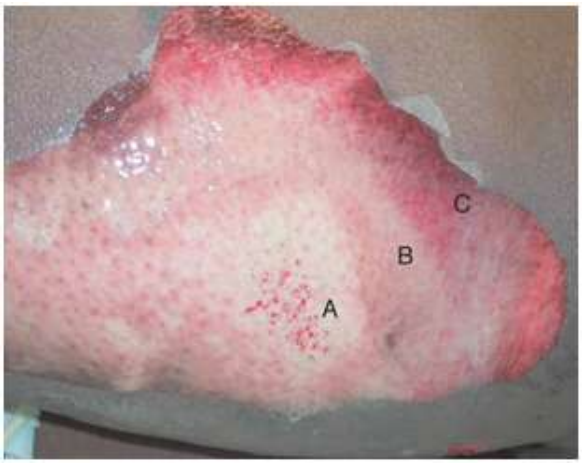

Figure 1: A) Coagulation Zone, B) Stasis Zone, C) Hyperemic Zone [5]

In first-degree burns, healing is by primary intention that takes 3 to 4 days without scarring. Second-degree superficial burns heal from epithelium of hair follicle remnants that are plenty in the superficial dermis. Healing process is complete within 2-3 weeks without scar formation and functional impairment. Both second-degree deep and third-degree burns healing process involves epithelisation and contraction. Healing process usually takes 3-8 weeks if not infected, with severe scarring, contraction and function impairment [5,9].

The wound healing process is a dynamic phenomenon that can be classified into 3 phases such as inflammatory/reactive phase, proliferative/reparative phase and maturation/remodeling phase, same like the other type of wound but with different duration. Inflammatory phase usually begin immediately after the injury that consists of vascular and cellular properties.Local vasodilatation with extravasation of fluid occurs after the injury. Capillary permeability is increased in extensive burn injury that may be leading to massive extravasation of plasma that requiring fluid replacement.Neutrophils and monocytes are the first cellular components that migrate to the inflammation site that later replaced by macrophages. The migration process of these cells is triggered by chemotactic factors like kallkireins and fibrin peptides and substances released from the mast cells likehistamine, tumour necrosis factor, proteases, leukotreins and cytokines [9].

Proliferative phase in partial thickness burns initiated by keratinocyte migration from viable skin appendages in dermis few hours after injury which ultimately leads to the basement membrane zone formation between dermis and epidermis. Dermal reconstitution is supported by angiogenesis and fibrogenesis. After primary excision and grafting as the part of proliferative phase in deep-burns, healing is mediated by delayed primary intention [9].

Remodeling phase is the final phase of wound healing which is marked by the maturation of graft or scar formation. There are some fibrous structural proteins i.e., collagen from type III and type I as well as elastin around epithelial, endothelial and smooth muscle as extracellular matrix. This extracellular matrix remodels into scar tissue and fibroblast become myofibroblast phenotype which is involved in scar contraction in resolution phase [9].

Skin Regeneration

The skin is composed of two layers: the epidermis and the dermis, these layers are connected by a structure named the Basement Membrane Zone (BMZ). The epidermis is fetal ectoderm that has regeneration ability that has several distinct layers. The main cell that form the epidermis is keratinocytes, melanocytes, Langerhans cells and Merkels cells. The dermis is composed of extracellular matrix and skin appendages with fibroblast, adipocytes and macrophages as the component cells [5,10].

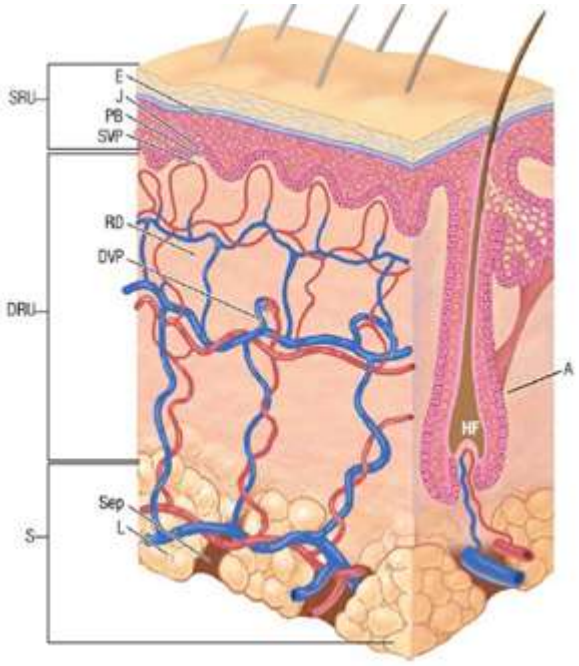

Figure 2: SRU (Skin Reactive Unit) consists of the epidermis (E), the junction zone (J), the papillary body (PB) and the superficial microvascular plexus (SVP). DRU (The Dermal Reactive Unit) consists of the reticular dermis (RD) and the deep microvascular plexus (DVP). The third unit is subcutaneous tissue (S) that comprises of lobules (L) and septae (S). The last unit is the appendages such as A; hair and sebaceous glands. HF (hair follicle) [11].

Cutaneous stem cells consist of epidermal stem cells (interfollicular and bulge stem cells), dermal stem cells, sebaceous stem cells, hair follicle stem cells, sweat gland stem cells, melanocyte stem cells, mesenchymal stem cells, neural stem cells as well as endothelial stem cells. The roles of thesecells are for skin homeostasis maintenance and hair regeneration and also participate in promoting epidermis repairmen after trauma. Most skin stem cells are located in the hair follicle bulge. They give rise to the daughter skin cells in order to migrate to the epidermis (basal layer and sebaceous gland), initiating the healing process and re-epithelialize a wound. In adult skin, superficial burn wound that doesn't affecthair follicles are usually healed through the regeneration of epidermal appendages. Deeper woundthat damaging the hair follicle bulge heal with a scar and without adnexal structures [5,10].

3. Stem Cell Therapy

Stem cells are characterized by prolonged self-proliferation and asymmetric replication. Asymmetric replication means that one of the cells retain its self-regeneration capacity in every cell division, while the other cells enter a differentiation pathway and join a mature non-dividing population (Figure 3) [12].

The ability of stem cells to differentiate into cells with specialized functions including keratinocytes is the reason that stem cells has potential for treating burn wound. There are two types of stem cells based on their origin: embryonic (ESCs) and non-embryonic stem cells/Adult Stem Cell (ASCs)/somatic stem cells.[4] ESCs is the most primitive form of stem cells that can be found in early form of embryo, called blastocyst. These cells has capability to differentiate into any cells from the human three embryonic layer (exoderm, mesoderm and endoderm). The clinical use of human embryonic stem cells is controversial due to ethical issue as well as safety reasons because it requires an embryo destruction, may develop teratocarcinomas, are immunogenic and show genetic instability *in vitro*[4,12,13,14].

The most ideal source for stem cell therapy must covers several criteria such as abundantly available, easy to be harvested with minimally invasive procedure, and can be transplanted to either an autologous or allogeneic host both safely and effectively. The main focus of stem cell therapy in burn injury is not only to get a faster and better re-epithelialization, but also targeting in reconstruction of skin appendages.[4] Due to several issues related to the clinical use of ESCs, the study about ASCs and Induced Pluripotent Stem Cells (iPSC) is more favored.

ASCs comprise of mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), epithelial and neural stem cells, and others. The characteristics of ASCs are thought to be tissue specific, capable to differentiate towards specialized cell types of the tissue or organ. ASCs have been identified in several organs and tissues such as: brain, bone marrow, blood vessels, skeletal muscle, skin, heart, liver, ovarian epithelium, gut and testis while they are found in an abundance in umbilical cord. They also tend to reside in a specific area of each tissue (stem cell niche). Compared to the ESCs, ASCs are less potent and have less differentiation potential as well as not capable of unlimited expansion *in vitro*[4].

Another scientific breakthrough in regenerative medicine is the founding of iPSCs that represent the ESCs or "artificial ESCs". iPSCs have the same ability to differentiate into almost all kinds of cells as ESCs without having to face the ethical issue; although, they share the common disadvantages of ESCs to develop malignancy. Some studies has demonstrated that ESCs can also differentiate into keratinocytes and can be used to grow epidermis *in vitro* as well as providing temporary skin substitutes. Aside from that invention, there is no clear advantage of using ESC or iPSC-derived skin substitutes for burn type of wound because generating these stem cells is relative time-consuming, labor-intensive and not cost-effective [4,12]

4. Mesenchymal Stem Cell for Burn Injury

Mesenchymal Stem Cell Characteristic and Source

Mesenchymal Stem Cells (MSCs) are a heterogeneous population of multipotent ASCs that can be found in various tissues or organs, such as bone marrow MSCs (BM-MSCs), umbilical cord MSCs (UCMSCs) and adipose MSCs (ADSCs). MSCs have the capability to differentiate into cells within the mesodermal, ectodermal and endodermal lineage and are abundantly available in human tissue. MSCs can differentiate into many kind of tissue like bone, cartilage, muscle, neurons, liver cells, cardiocyte and so on [15].

MSCs becomes the most realistic and potential stem cell type because their plasticity in tissue repair and regeneration. They promote wound healing and regeneration by differentiate into tissue-specific cells and through the paracrine effect that stimulate the survival and functional recovery of the resident cells. MSCs also have immune regulatory potency other than their low immunogenicity nature. That ability enables the modulation of the local microenvironment

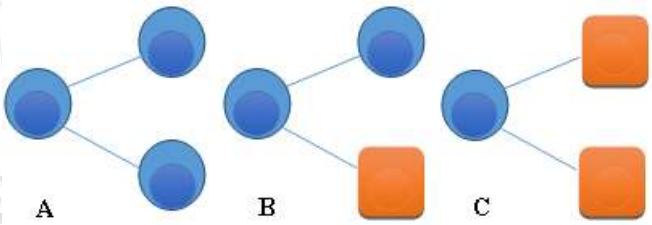

Figure 3: A) Symetric Self-Renewal, B) Asymetric Self-Renewal, C) Symetric Differentiation.

and the host immune response result in angiogenesis enhancement and immune response suppression. Those features hold fundamental implications for clinical applications in burn wound therapy [15].

Among different sources of MSCs, BM-MSCsare thought to be the key role in wound healing including burn wound type as they are found in skin epidermis by several studies. A study by Xue, *et al.*shows that 30 mice with post escharectomy burn wound that are injected with BM-MSCs heal significantly faster in day 20 than control group with average time healing 25 days.The result of RT-PCR and western blotting were observed to see angiogenesis process, Ang-1/2, CD31 and VEGF as the specific markers of new vessel were expressed in both the BM-MSC and control groups, but was much stronger in the BM-MSC group [12.15].

Compared to the painful procedure of bone marrow retrieval, ADSCs are more accessible than the other derivation of MSCs as they are available in adipose tissue throughout the human body and no overly invasive procedure required to harvest those cells. Karimi, *et al.*demonstrate that the wound surface area and eschar thickness were smaller in the mice with third degree burn that are injected by 1cc of the ADSCs than the control group, although there was no significant difference for decreasing values of wound area characteristics between the groups [16].

UCMSCs also shows promising potential in tissue regeneration related to their *in vitro* expansion capacity, multipotency and immuneregulation features. UCMSCs are found to have similar functional characteristics and immune phenotypic to the BM-MSCs [14].A study by Liu, *et al.*conclude that transplantation of UCMSCs in severe burn rat model can improve the wound healing as the cells migrated into the wound and decrease several infiltrated inflammatory factors as well as levels of pro-inflammatory factors like IL-1, IL-6 and TNF-a. In contrast, it also increase the level of anti-inflammatory cytokines like IL-10 and TSG-6. It also found an enhancement of collagen type I and III ratio that facilitate wound healing process. The advantages of using human umbilical cord MSCs (hUCMSCs) are their short amplification time, high proliferation rate, lower immunogenicity, abundance, and convenience compared to other original MSCs [17].

Delivery Strategy of Transplantation of MSCs in Burn Therapy

The vulnerable survival rate of MSCs at the transplanted site often reduce their therapeutic potential. Further investigation needs to be done to enhance the survival rate of transplanted MSCs and the secretion of factors and ultimately, their biological functions [18].Some stem cells administration strategies for skin regeneration have been described such as local and systemic route as well as combined injection and with scaffolds [10]. Here are some strategies that have been done in several studies to use stem cells in skin wound:

Local Delivery

Kim, *et al.* evaluated the effects of of topical BM-MSCs transplantation in experimental full-thickness cutaneous wounds of beagle dogs. BM-MSCs diluted in phosphate-buffered saline (PBS) and PBS only as the vehicle control were injected intradermally into the wound and the wound closure process was analyzed histologically. MSCs-treated lesions showed faster wound closure and increased collagen synthesis as well as cellular proliferation and angiogenesis thatwas evaluated by immunocytochemistry compared to vehicle-treated lesions. In addition, MSC-treated lesions also showed decreased expression of wound healing related factors (basic fibroblast growth factor and matrix metalloproteinase-2) and pro-inflammatory cytokines (interleukin-2 and interferon-c) [19].

Forcheron, *et al.*examined the underlying mechanism of Cutaneous Radiation Syndrome (CRS) recovery treated by intradermally injected autologous BM-MSCs in a minipigs model. Those minipigs were observed three times a week and inflammation process was assessed with thermal camera. They found that MSCs injection result in local accumulation of lymphocytes at the dermis/subcutis border and improved vascularitation. In the end, they concluded that stem cell therapy can be applied as the treatment of human CRS [20]

Combined Injection

Nakamura, *et al.* performed study that evaluated the therapeutic effect of topical administration of BM-MSCsgenetically engineered Stromal Cell-Derived Factor-1 (SDF-1) on a full-thickness wound model of rats. There were three groups of rats where MSC or SDF-MSC in PBS or PBS alone were injected subcutaneously around the wound. In vitro cell migration assay showed that the SDF-1-engineered MSC (SDF-MSC) improved the migration of MSC and dermal fibroblasts in a greater amount than MSC treatment alone. The SDF-MSC also found to secretemore vascular endothelial growth factors, hepatocyte growth factors, and interleukin 6 resulting in more rapid closure of wound compared to MSC and PBS treatments. The other findings were significantly larger neoepithelium's length and the greater number of newly formed blood vessel as well as the improvement of SDF-MSC survival rate in the tissue [18].

A study by Kim, *et al.* investigated the therapeutic potential of mesenchymal stem cells (MSCs) combined with human amniotic membrane (HAM) when grafted into full thickness skin defects of rabbits model. One of the main components of the amniotic basement membrane is laminin that play role in cell differentiation, shape and movement, the maintenance of tissue function as well as tissue survival promotion. Full-thickness skin defects which were excised by surgical procedure in four groups consists of five rabbits respectively were covered with HAM and sutured by using 5–0 nylon. Among those two groups that were grafted with HAM, group A was previously loaded with autologous MSCs and group B with allologous MSCs. The other groups were subsequently injected with autologous MSCs (group C) or allologous MSCs (group D) beneath the amniotic membrane. The wounds were observed at 7, 12 and 15 days where the group loaded with MSCs showed statistically significant improvements of wound healing with no significant difference between autologous and allologous group [21].

Intravenous Route

A study conducted by Liu, *et al.* performed intravenous injection of hUC-MSCs into the adult male Wistar rats with severe burns and the wound closurewas assessed with Image Pro Plus. They concluded that the wound healing process was significantly accelerated in those rats as the eschar were completely desquamated while there's no sign of severe infection that can caused delayed healing at week 2. They also found that hUC-MSCs have capability to modify collagen type I and III accumulation and upregulated their ratio in severe burn [17].

Similar study using rat model was demonstrated by Singer, *et al.* showed that intravenous injection of rat BM-MSCs can delayed the progression of burn injury in a rat comb-burn model assessed from the area of necrotic. Twenty rats model were injected by rat-specific MSCs 60 minutes after injury and observed for 7 days. The interspaces of the comb-burn became totally necrosis and did not increase in severity in any of the animals at day 4. At day 7, approximately 80% of the combined area of the burn interspaces underwent necrosis in experimental group while in the control group was 100% [22].

Besindhoum, *et al.* have also been used intravenous route for BM-MSCs transplantation to treat radiation-induced complications that caused by radiotherapy. Irradiated mice

were received intravenously infused MSCs 24 hours after injury (30 Gy locally on the thigh) resulted in a decrease of the damage and acceleration ofthe healing process [23].

MSCs with Scaffold

Most of the current researches aim to determine the most appropriate and effective scaffold to improve MSCs' viability, improve cell attachment, support the growth and nutrition supply of the implanted cells [7,23].Formigli, *et al.* evaluated the effect of BM-MSCs seeded on bioengineered scaffolds Integra + Platelet-Rich Plasma (PRP) (Ematrix) to improve wound healing process in rats model. The experiment result showed that MSCs-seeded scaffold greatly improved the quality of skin regeneration, reduced collagen deposition, enhanced neo-angiogenesis and reepithelization as well as restored the damaged hair follicles and sebaceous glands. It is believed that paracrine activity is the underlying mechanism in modulating the wound healing response. Morover, it was also found that MSC-seeded scaffolds also increased the expression of Matrix Metalloproteinase 9 (MMP9) in the extracellular matrix and improved the recruitment of endogenous progenitors during tissue repair [24].

Another study using MSCs with scaffold to treat burn wounds is an experiment by Liu, *et al.*that compared the effectiveness of Tissue-Engineered (TE) skin containing MSCs, Collagen-GAG as scaffold only, and control group (no graft) to treat deep partial thickness burns in porcine models. Collagen is often used as the material for TE skin because of its low antigenicity and high growth promotion features. TE skin is composed of collagen scaffolds and MSCs could give the dermal component to inhibit wound contraction and an epidermal component to close the wound. In this study, TE skin containing MSCs showed more rapid healing and keratinization, less wound contraction, and more neovascularization that is important for dermal regeneration [25].

5. Conclusion

Skin is the largest organ of the human body which extreme loss of skin due to burn injury can cause substantial physiological imbalance and devastating cosmetic effect. While skin grafting is commonly used for treating major burn injury, it has some postoperative complications. Stem cells therapy has been considered to be an alternative approach for treating burns especially MSCs that are abundantly available through the human tissue. Some MSCs sources that are commonly used for burns are BM-MSCs, ADSCs and hUC-MSCs while the delivery routes are local injection, combined injection, systemic and MSCs transplantation with scaffold. Current researches focus in finding the best strategies for MSCs deliveries into the wound to increase MSCs viability rate and therapeutic potential. Further study needs to be done to investigate the best source of MSCs, MSCs delivery strategy, comparison between each source and strategy as well as its safety and long-term effect.

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