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Importance of Stem Cell Therapies and Their Applications in Wound Healing

The process of wound healing involves multiple, intricate mechanisms that are able to coordinate an effective response which maintains tissue integrity and homeostasis through allostatic response to injury. Previous studies have established that the wound repair process begins with an inflammatory response from the immune system, and its completion results in previously healthy tissue being replaced by patches of fibroblasts and a disorganized extracellular matrix consisting of collagen; ultimately, this process results in scar formation. (1,2) Additionally, wounds also play a causal role in lacerations, ulcers and even diabetes. Thus, in the past 30 years, wound healing has been identified as a key target for research due to variety of health issues that arise due to different types of wounds. (3) Throughout this period of research, researchers have shown that the application of stem cells in wound healing holds much promise in advancing current therapies. This paper aims to overview the need for stem cells and their current uses in wound healing.

Importance of Wound Healing

Wound repair typically occurs in the majority of tissues after any disruption of tissue integrity. (1) Thus, epithelial wound treatment comprises a large portion of the current healthcare system, intimately linked to surgical/accidental

lacerations, burns, pressure/venous ulcers, diabetic ulcers, and various types of scarring. It is estimated that the treatment of wounds and other secondarily associated complications exceeds 20 billion dollars annually. (4) Chronic wounds are especially costly, as they will require repeated bouts of treatment; it is estimated that 1% of the population at any given time is suffering from some form of chronic wounding. (5) One of the foremost issues with wounds comes in the forms of hypertrophic scarring, which can result in permanent functional loss as well as stigma from society. (6) Hypertrophic scars are usually the result of traumatic injuries or burns, and with almost 1 million people requiring treatment for burns, 2 million injured in motor accidents, and 34 million related surgical procedures being performed annually, it is clear that this is a pressing issue. (6,7) Hypertrophic scarring is linked to over-proliferation of inflammatory cells and fibroblasts during the wound healing process, further contributing to a highly disorganized matrix structure, which is characteristic of scars. (8) Hypertrophic scarring currently has no known cure, and the current treatments do not alleviate the aesthetic issues that accompany the scarring; therefore, hypertrophic scarring makes an excellent target for stem cell therapies.

In addition to hypertrophic scarring another wound-related affliction is keloid scarring. Keloid scarring occurs only in humans and only in response to injury. (9) They are defined as scar tissue that progressively invades surrounding normal tissue. Surgical incisions or sutured wounds are often causes of keloid scarring as well. Keloid scars will not regress back into the skin over time, as is characteristic with hypertrophic scars, thus causing aesthetic problems for the

patient. In fact, the amount of scar tissue formed does not correlate to the severity of the initial wounding, so even small wounds can have catastrophic consequences. Although multiple types of treatments have been attempted with keloid scarring, none have yielded significant results. (10, 11)

Furthermore, chronic wounds have shown to cost billions of dollars annually in treatment, marking them as an important target for future therapies. While properly healed acute wounds leave behind a benign scar, if they are not adequately healed they can lead to an undesirable scar or even a chronic, nonhealing wound. Failure of correct healing can be attributed to aging, sedentary lifestyle, psychological factor, smoking, and many other conditions. (12) However, a key condition that is tightly linked to chronic wounds is diabetes. There are a number of differences in diabetics (such as impaired ability of neutrophils and macrophages to migrate to the wound site) that result in delayed wound healing, making them more likely to develop foot ulcers. It is then possible that infection can take hold in the wound and result in the need for amputation. Ultimately, a better understanding of the mechanisms behind chronic wounding allied with stem cell therapy could help save millions in costs to patients and significantly increase the quality of life for these patients. (13)

Pathophysiology of Normal Wound Healing

The normal wound healing process can be broken down into three primary stages: 1) inflammatory phase, 2) proliferation phase, and 3) maturation phase. It is important to understand the correct observed mechanisms for wound

healing in order to understand abnormalities associated with various wound-healing disorders and how to treat them.

The inflammatory phase is characterized by coagulation of blood, which leads to the formation of a blood clot that covers the wound. Blood flow is often restricted within the wound area, but it is significantly higher in the surrounding area. This results in the release of inflammatory factors such as histamine, which also create a fibrin matrix. These steps account for the swelling and redness often observed in the initial stages of wound healing. Once the matrix is established, neutrophils will enter to remove the dead tissue, and attempt to control any potential infections via adaptive and innate immune response. This phase typically lasts 4 days. (14,15)

In the proliferation phase, the inflammatory cells will release a wide array of signals and factors that will recruit fibroblasts and vascular endothelial cells to the wound site. Fibroblasts will release collagen, which will start to replace the fibrin matrix, and increase the mechanical strength of the wound. Some of the fibroblasts may also differentiate into myofibroblasts, which will allow the wound to contract reducing healing area. The vascular endothelial cells will invade via angiogenesis and form granulation tissue. Keratinocytes will also move to the edges of the wound site and begin to proliferate. If the wound has destroyed the follicles, reepithelialization will be very slow or a graft may be required. (14,16)

In the maturation phase, the wound will have reepithelialized. The dermis will also have regained most of its tensile strength, however, it will not be anywhere near as elastic as it originally was due to extensive fibrosis. Most of the

endothelial cells, macrophages, and myofibroblasts will undergo apoptosis as the healing processes wind down. The final scar will still undergo further remodeling over many months to years. (14,17)

Traditional Approaches to Wound Healing

Traditionally, deep wounds had poor healing results due to the destruction of keratinocytes in the dermis, which are responsible for forming the epithelium. Faced with this problem, surgeons found the answer in the form of skin grafts, specifically autografts. Since the patient will be donating his or her own tissue, there will be no fear of rejection from the host body and no need for immunosuppressants such as cyclosporin. Typically this procedure involved removing a thin layer of skin with all the epidermis intact and part of the dermis from the donor site. This became known as a split-thickness graft, and it was subsequently stretched over the wound site using a mesh framework. (18) Surgeons noticed that they required the maximum amount of dermis they could harvest from the donor site to increase the effectiveness of the graft. (19) If, however, it was not possible to harvest skin for an autograft or there was no donor skin available, surgeons had to use allografts or xenografts. Allografts are harvested postmortem from consenting donors, and xenografts are made from pig skin. These were only temporary measures to provide growth factors for wound healing, as the host body would begin to reject these grafts almost a week after they were implanted. (20)

The issues with grafts using donor tissue were apparent, so researchers responded by creating tissue engineered skin substitutes. The first of this type

were known as matrix-based products, which are still used even today. These matrices were implanted into the wound bed, where they essentially functioned as templates for revascularization. However, even these engineered substitutes needed to eventually be covered with autografts in order for complete dermal regeneration. (21) Finally, there were cell-based treatments, where keratinocytes were harvested from patients and then subsequently expanded via cell culture *in vitro*. The process ultimately resulted in an autologous epidermis for the patient; however, the product is very thin, fragile, and relatively expensive to produce. (22)

It is clear that there have been multiple attempts to increase the effectiveness of wound healing techniques, as well as create more efficient and reliable grafts. Unfortunately, even the most advanced engineered skin substitutes still pose many challenges; they are very expensive, not always very effective, and they cannot completely reconstitute skin appendages. These associated problems make it clear that a different approach to wound healing is necessary in order to create more pragmatic and effective solutions to wound-related issues. (23)

Stem Cells and Wound Healing

In order for cells to be classified as stem cells, they must meet two critical requirements: they must have a prolonged capacity for self-renewal and they must be able to employ asymmetric division to differentiate into more specialized cell types. (24). These characteristics endow a set of unique abilities in these types of cells, which could be harnessed to aid the regeneration and repair

process in damaged skin. Studies using models of tissue injury have shown severe injury has resulted in a dramatic increase in the number of stem cells in blood circulation. (25) Not only that, a similar study also showed that Green Fluorescent Protein (GFP) labeled bone marrow cells at the wound site, and they had differentiated into various lineages. (26) Other such findings also suggest that stem cells play a very important role in the process of wound healing, and further studies are needed to better understand the underlying mechanisms. In this section, I aim to elaborate on notable findings on the applications of mesenchymal stem cells (MSCs), adipose-derived stem cells (ASCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs) in wound healing.

The dominant majority of studies looking at potential stem cell related wound healing therapies have centered on adult stem cells, and specifically mesenchymal stem cells (MSCs). MSCs are able to self-renew and have shown great promise for treating tissue damage involving immune responses. (27, 28) MSCs can be harvested from a patient's bone marrow, adipose tissue, umbilical cord blood, and most importantly—dermis. (29) Since MSC implants have an insignificant immune reaction from the host, they are especially important for modulating wound repair. (28,30) Moreover, bone marrow-derived MSCs (BMSCs) have been shown to synthesize higher amounts of collagen, growth factors, and angiogenic factors than the native dermal fibroblasts which suggests that they could be implanted in wounds to increase the rate of healing without eliciting any immune response. Patients with leg ulcers showed successful

wound closure after treatment with collagen matrices with BMSCs implanted within. (31) Another study looked at using autologous skin fibroblasts with MSCs implanted on collagen membranes to treat diabetic patients with foot ulcers. As a result, the wound size decreased and the vascularity of the dermis increased significantly. (32) Though MSCs have demonstrated a consistent ability to increase the rate of wound healing in a variety of scenarios, there are still some drawbacks to MSC treatment. For example, MSCs are a practical approach to small wounds, but it is unfeasible to culture enough MSCs to apply to a large wound. Not only that, the population of MSCs within humans decreases over time, possibly eliminating the option of using autologous MSCs for treatment in the older generations. (33) Regardless, there is still significant evidence that shows these cells have the potential to contribute to both inflammatory and mesenchymal cells in the dermis, but also keratinocytes in the epidermis, which is why they are exciting targets for improving wound healing. (34)

Adipose tissue is an immensely complex tissue and comprises of adipocytes, smooth muscle cells, fibroblasts, macrophages, endothelial cells, and lymphocytes. Irrespective, the surgical procedure to access the subcutaneous adipose tissue is very simple, and the subsequent ASC harvest is also a relatively simple technique. Adipose-derived stem cells (ASCs) are pluripotent cells that have the potential to differentiate into bone, cartilage, tendons, and fat, when they are provided the correct nutrients and extracellular stimulation. They share an almost equal potential with MSCs to differentiate into cells of mesodermal origin, but are preferred because they are easier to access and

widely available. (35) In one study ASCs have been shown to promote human dermal fibroblast proliferation in the wound site by secretion of paracrine factors, which ultimately increased the rate of wound healing. (36) Another study showed that ASCs , under hypoxic conditions due to the inflammation, significantly increased the levels of collagen synthesis and helped reduce the wound area. Further study showed that this was achieved by up-regulation of imperative growth factors vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). (37) Thus, there is conclusive evidence that ASCs show immense promise in the future of wound healing treatments.

ESCs have been a topic of extreme controversy in the United States, and access to these cells in the past has been very limited. The embryo has an immense proliferative capacity, and therefore is often regarded as the key source for pluripotent stem cells, and if ethical issues are circumvented, they may prove to be imperative to understanding the biochemical mechanisms of wound repair. In terms of direct therapy, ESCs are not as useful as adult stem cells because most researchers have attempted to implant them into wounds, which would essentially duplicate the effect of an allogeneic graft. Allogeneic grafts are already available at a much more reasonable cost, so it is infeasible to pursue that avenue of research. However, some studies have shown that ESC-derived endothelial cells have the potential to secrete a variety of cytokine factors that are aid the wound healing process. (38)

Finally, the landmark study conducted by Yamanaka in 2007 described the method to reprogram adult cells to back to an embryonic state, opened up

many new avenues of research using induced pluripotent stem cells (iPSCs). (39) These cells can potentially overcome two challenges associated with ESCs: they are not shrouded in ethical controversy and also will not be subject an autoimmune response from the body. One study managed to reprogram dermal fibroblasts into iPSCs, without use of a viral vector, which meant that iPSCs could be derived for the sick and/or older patients who most likely need them more. (40) Another study has shown that iPSC-derived fibroblasts show an increased production of extracellular matrix proteins that could also increase the rate of wound healing. While iPSCs are being applied in countless other fields of research, there is still need of more effort to see if any iPSC-based therapies could significantly improve wound healing.

Thus, it is evident that the wound healing related issues result in billions of dollars being spent annually in remediation attempts and can cause immeasurable psychosocial pain to patients. Therefore, it is imperative that the older graft techniques be replaced by novel stem cell-based therapies that can increase the efficiency of wound healing as well as serve as a more practical solution to a widespread problem.

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