Review Article

Advances in Wound Healing and Wound Care Technologies – A Review

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ABSTRACT

Wound healing is a progressive and sequential series of events for the ultimate restoration of distressed tissue. Inflammation, tissue proliferation and remodulation are the three main phases involved in wound healing which is however preceded by a hemostasis phase which involves vasoconstriction, platelet aggregation and thrombus formation. The proliferation phase marks the formation of new cells and blood vessels and the overall process of wound healing is terminated by the remodulation phase, which involves the formation of new tissue made up of collagen fibers. Wounds are further classified as acute and chronic based on the duration taken for the healing process and the technologies involved in wound treatment intend to reduce the time taken to heal. To treat wounds, various wound care products have been developed such as negative pressure wound devices (NPWD), hyperbaric oxygen therapy, bioengineered skin substitutes, silk-based biomaterials and mesenchymal stem cells (MSCs)-based therapy. This review highlights the use of bioengineered skin substitutes, silk-based biomaterials and mesenchymal stem cells (MSCs) for treating wounds.

Keywords: Wound Healing, Wound Care, Skin Substitutes, Silk-based Biomaterials, Mesenchymal Stem Cells (MSCs)-based Therapy.

INTRODUCTION

The process of wound healing has been extensively studied for many years now. There have been advances in understanding the exact mechanisms involved in this process and the field of wound care is dependent on the understanding of the process of wound repair. Wounds are classified, based on how long they take to heal, as acute, wounds that heal within 10-12 weeks, and chronic wounds, which take more than 12 weeks to heal and it is based on this classification that the wound care technologies are developed. Wound care has improved greatly over the years and now, the field of wound care has a tremendous number of treatment options. New wound care products stimulate the synthesis of collagen, promote angiogenesis and increase the rate of re-epithelialization. Latest technologies are based on manipulating the wound environment. While the well-established techniques are still followed, new technologies have developed and many new products have been introduced into the market. There is a continuous advancement in the production of better and more efficient technologies to treat wounds.

This review will discuss the overall mechanism involved in the process of wound healing and will highlight three new prominent technologies involved in wound care. Bioengineered skin substitutes, silk-based biomaterials and mesenchymal stem cells have gained attention over the years due to their great potential to treat wounds and have henceforth been elaborated in this article.

WOUND HEALING MECHANISM

Wound healing is a forced response including a cascade of events to orchestrate smooth progression and restoration of tissue. Three significant phases of wound healing are Inflammation, tissue proliferation and remodulation. These events are not time constricted; as they overlap and include systematic series of processes such as clotting, inflammation, granulation, tissue formation, epithelialization, neovascularization, collagen formation and wound contraction.[1,2]When cells experience damage associated or pathogen-specific molecular patterns, the primary sensory neurons facilitate immediate response by transmigrating mononuclear cells to the site to secrete inflammatory cytokines.[3,4] Hemostasis is a partial modulatory phase before inflammation; which facilitate vasoconstriction, platelet aggregation and thrombus formation for the infiltration of cells.[5,6] Neutrophils eliminate the pathogens in the site while chemoattractants like Transforming growth factor-β (TGF-β) and monocyte chemoattractant protein-1(MCP-1) attract monocytes to the wound site, and cumulating its conversion to macrophages for the further proliferation phase.

Proliferative phase involves the formation of new cells and angiogenesis by endothelial cells, fibroblasts and keratinocytes. Reactive oxygen species (ROS) sequester the supply of blood to healing areas and supply phagocytic and bacteriostatic effects to the surrounding environment.[7,8] Macrophages and platelets deliver essential growth factors and pro-inflammatory cytokines and all these, lead to the production of extracellular matrix and collagen fibers by fibroblasts and myofibroblast. Angiogenesis enhances tissue granulation and re-

epithelialization, which contributes to 80% wound closure in humans.[9,10]

The remodulation is the longest and demarcation phase which take even years to complete. This phase starts after 2-3 weeks, resulting in the restoration of wounded original tissue with a collagenous scar without any epidermal appendages. The ultimate aim of remodulation is wound closure by the formation of a densely packed, less vascular neotissue made of parallel collagen fibers.[11-13] This is characterized by an increased amount of type I collagen, produced by myofibroblasts and formation of keratinocytes as layers. The active cells present during proliferative phase undergo either withdrawal, or apoptosis, or degraded by the plasmatic metalloproteinases.[14-17] This accounts for the initial redness of scars and the hypopigmentation upon maturation. The various stages of the wound healing processcan be visualized in figure 1.

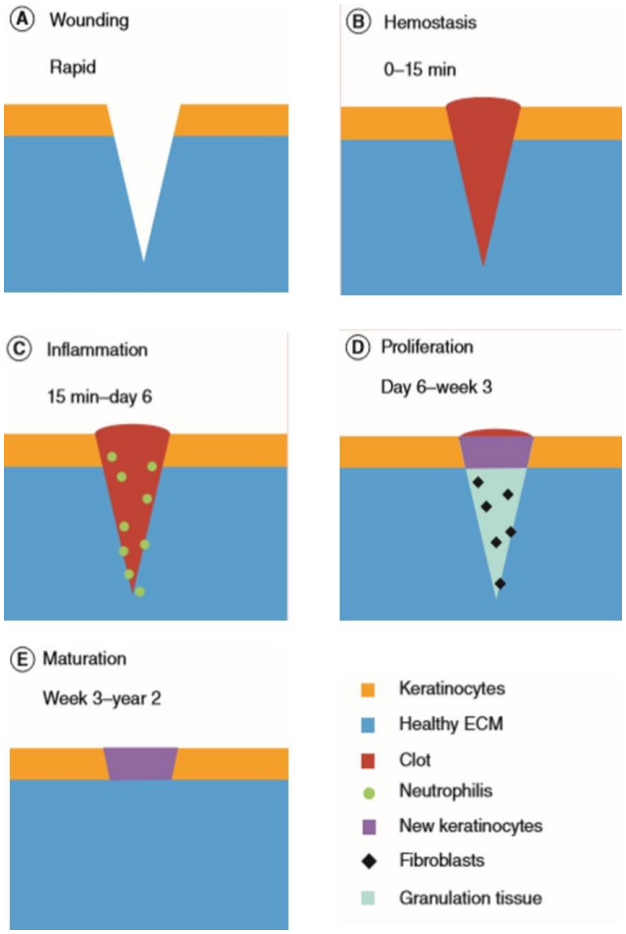

Figure 1: Successive stages of Wound healing. a) Wounding: occurrence of a wound in healthy tissue. b) Hemostasis: clot formation. c) Inflammation: Elimination of pathogens in the injured site by neutrophils. d) Proliferation: Occurrence of granulation tissue and keratinocytes, infiltration of fibroblasts. e) Maturation: The final phase, fibroblasts disappear and formation of healthy ECM.[18]

ADVANCES IN WOUND CARE TECHNOLOGIES

Wound care is one of the emerging and affluent sectors in the medical field. The wound care armamentarium started back in 69 BC when people used silver to treat infections.[19] This domain has changed immensely over past decades due to the furtherance in technology and evolved in the usage of personalized medicine according to its idiosyncratic phenotype.

Negative Pressure Wound Devices (NPWD) have been used from the onset of the 21st century and is still prevalent in populations.[19] This can be used for soft tissue injuries, pathogen-infected wounds, debridement wounds as well as enterocutaneous fistulas.

Hyperbaric oxygen therapy has been widely used in recalcitrant wounds, mainly DFU. This can assist angiogenesis, growth factor signaling, cellular mobility, fibroblast proliferation and enhance leukocyte function.[20-22] This therapy also inhibits the spreading of infectious necrosis due to high level oxygen.[22]

Manipulation of Reactive Oxygen Species (ROS) in wound therapy is another approach where they are dispensed to stimulate angiogenesis, cellular migration as well as to provide bacteriostatic effect to wound microenvironment. But this technique is far more useful in acute wounds and its critical concentration in treatment hinders its wide usage.[7,8]

An establishing method in chronic wound treatment, mainly DFU, is Cell-based therapy; application of healthy, donor-derived mesenchymal stem cells (MSC) into the circulation. The stem cells of diabetics or chronic wound patients are defective so that the administration of these MSC could help in normal restorative healing of wounds.[23,24]

The use of bioengineered skin substitutes, silk-based biomaterials and mesenchymal stem cells in wound treatment are described below.

Bioengineered Skin Substitutes

Bioengineered skin substitutes may be produced either as cellularized engineered skin grafts or as acellular dermal regeneration templates (DRTs). These have been developed to take care of two main problems affecting the wound repair mechanism in cases of deeper wounds, which are, reducing the quantity of healthy skin removed from the patient and restoring the skin's physiological conditions avoiding scar formation.[25-34]DRTs are made up of porous and fibrous materials and are nothing but a 3D scaffold which mimic the 3D architecture of human tissue to support cell growth. The DRTs must be non-immunogenic, biocompatible, stiff and flexible and should support epidermal growth and promote the influx of blood vessels once implanted.[35-37]

Acellular Dermal Substitutes: Acellular matrices provide a natural 3D environment for the endothelial and fibroblast cells to invade and promote new extracellular matrix and

form a vascular network.[25] Some of the commercially available acellular dermal substitutes (**Table 1**) are described below.

Alloderm, Dermacell and Dermamatrix are non-crosslinked, decellularized dermis, obtained from cadavers, which can be inserted in the wound bed.[28,30-33,37-40] Alloderm is being used for burn victims since 1992 and it has also been used for the treatment of severe soft tissue defects.[41] The structure of Alloderm can be seen in **figure 2**. Dermacell and Dermamatrix are intended for soft tissue reconstruction (abdomen, nasal reconstruction, facial defects, etc.) and for reconstructing breast.[25] Integra is made up of bi-layered extracellular matrix fibers which are of cross-linked bovine collagen and chondroitin-6-sulphate with a transient epithelium made using a silicone membrane. The structure of Integra can be seen in **figure 2**. The silicone sheet is taken off only after the formation of neodermis.[33,41,42] The vascularization is faster in Matriderm than in Integra. This is because of the presence of elastin in Matriderm, which attracts more vascular cells than Integra.[25] Some of the commercially available products are listed along with their composition and applications in **table 1**.

Cellularized Dermal Substitutes: Cellularized skin substitutes can be categorized into three: (1) Epithelial sheets: formed by seeding epithelial cells on polymeric membranes. (2) Dermis equivalents: composed of fibroblasts contained generally in either 3D porous matrices or hydrogels. (3) Full-thickness (or composite) equivalents: composed of an epidermis and dermis equivalent. A few commercially available cellularized dermal substitutes (**Table 2**) are described below.

Dermagraft is made up of a bio-degradable PLGA mesh which is seeded with cryopreserved neonatal allogenic fibroblasts. This material is advised to be used in patients with sufficient blood supply.[44] The structure of Dermagraft can be seen in **figure 2**. TransCyte consists of a mesh (made up of nylon) coated with bovine collagen which is seeded with neonatal allogenic human fibroblasts which synthesize extracellular matrix components along with growth factors.[45] The structure of TransCyte can be seen in **figure 2**. OrCel is a bi-layered skin substitute composed of human fibroblasts in a bovine collagen sponge. OrCel, after being placed in the wound site, dissolves and gets replaced by the patient's skin.[27,45,46-49]Apligraft is made up of neonatal fibroblast cells which are seeded on a bovine type I collagen gel with neonatal keratinocytes being cultured on top of this dermal layer.[47,50,51]The structure of Apligraft can be seen in **figure 2**. Some of the commercially available products are listed along with their composition and applications in **table 2**.

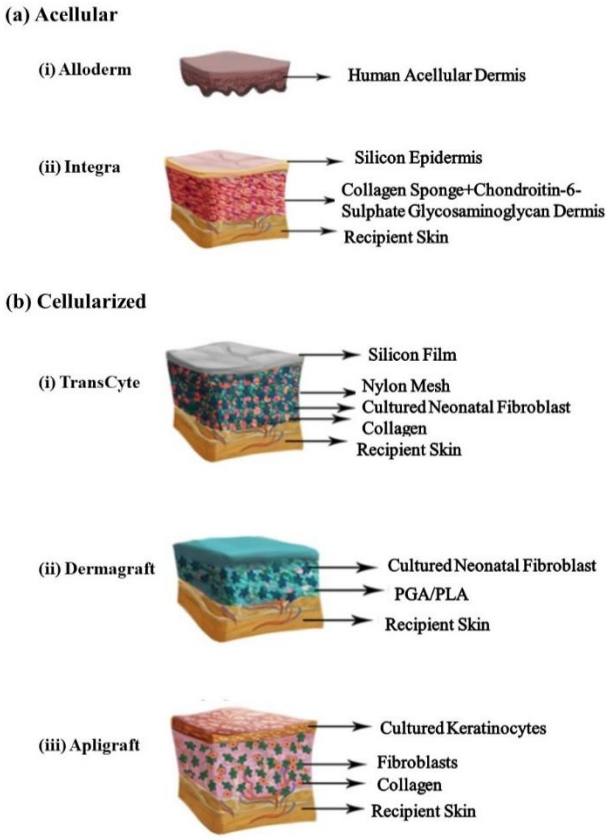

Figure 2: Bioengineered Skin Substitutes. (a) Acellular: (i) Alloderm, (ii) Integra; (b) Cellularized: (i) TransCyte, (ii) Dermagraft, (iii) Apligraft.[52]

Table 1: Acellular Dermal Substitutes[25,43]

Product	Graft	Composition	Application
Alloderm	Allograft	Acellular Human Dermis, Non-crosslinked	Soft Tissue Reconstruction
Dermacell	Allograft	Acellular Human Dermis, Non-crosslinked	Chronic Non-healing Wounds
Dermamatrix	Allograft	Acellular Human Dermis, Non-crosslinked	Soft Tissue Replacement, Breast Reconstruction
Integra	Xenograft	Acellular Bovine Type I Collagen and Chondroitin-6-sulphate Copolymer coated with a Thin Silicone Elastomer, Crosslinked	Deep Partial Thickness and Full Thickness Burns
Matriderm	Xenograft	Bovine Non-crosslinked Lyophilized Dermis coated with Elastin Hydrolysate	Full Thickness Burns

Table 2: Cellularized Dermal Substitutes[25,43]

Product	Composition	Application
Dermagraft	Human Cultured Neonatal Fibroblasts Seeded on Polyglactin Scaffold	Diabetic Foot Ulcers
Transcyte	Nylon Mesh Coated with Bovine Collagen and Seeded with Allogenic Neonatal Human Foreskin Fibroblasts	Full and Partial Thickness Burns
Denovoderm	Autologous Fibroblasts in Collagen Hydrogel	Deep Defect of Skin
Orcel	Type I Bovine Collagen Matrix Seeded with Allogenic Neonatal Foreskin Fibroblasts and Keratinocyte	Epidermolysis Bullosa
Apligraft	Bovine Collagen Matrix Seeded with Neonatal Foreskin Fibroblasts and Keratinocytes	Diabetic and Venous Ulcers, Epidermolysis Bullosa

Silk-based Biomaterials

Scaffolds that are derived from silk are said to be biodegradable, biocompatible and also believed to mimic the extracellular matrix of the skin.[49,54] Their porosity and good mechanical strength, along with the cellular and molecular modulators which promote tissue redevelopment, help them create an excellent microenvironment for wound healing.[55] Among most of the biomaterials reported, silk fibroin from *Bombyx mori* (mulberry silkworm) has been widely accepted as a material for applications in the biomedical field due to its biodegradability, low immunogenicity, biocompatibility, cost-effectiveness, tensile properties and easy processing.[56,57] Silk is made up of two proteins, a central protein called fibroin and a glue-like coating called sericin.[58] The structure of silk fiber can be seen in **figure 3**. Biocompatibility problems have been reported to be caused by sericin and sericin-free silk fibroin is reported to show excellent biocompatibility.[54,58-61] Electrospinning biocompatible polymers (natural and synthetic) hold great potential in the field of wound healing as it closely mimics the structure of the natural ECM and also allows to incorporate bioactive molecules easily.[56,62-64]

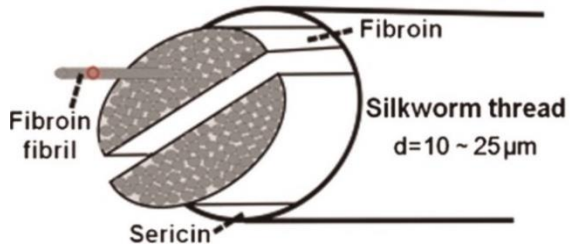

Figure 3: Structure of Silk Fiber[56]

Silk Fibroin-based Biomaterials: Silk fibroin-based biomaterials were reported to have great mechanical properties.[53,54,59,65,66] Studies have stated that silk fibroin blends show good biocompatibility[53,54,59,65] and also that silk fibroin when used in vivo, doesn't induce any significant immune response.[54,59,67,68] Also it has been shown that there was no trace of thrombus formation when sutures coated with fibroin were introduced into animal connective tissue, which confirms its blood compatibility.[65,69] Silk fibroin-blended materials are ideal biomaterials as they also have high porosity.[53,54,59,70-73]

The disadvantages of silk fibroin-based biomaterials have also been stated by many. Dry state pure silk fibroin films cannot be used for wound care as they have poor mechanical properties.[23,65] Electrospinning silk fibroin nanofibers can increase the porosity of the material but, this also provides bacteria with a suitable growth environment.[19,31,59,75] When using a regenerated silk fibroin, it is difficult to produce a uniformly thick material as its brittleness causes it to fragment easily.[24,32,53,64] Antimicrobial effect is absent in silk[65,76] and hence, many studies blend another polymer, which is enriched with antimicrobials or antibiotics such as an antimicrobial peptide[59] and vancomycin[73], with silk.

Silk Sericin-based Biomaterials: Two silk fibroins are joined together by a natural polymer called silk sericin to form silk yarn. Silk sericin is highly hydrophilic and it can be cross-linked with other polymers due to its organization, solubility and structural composition[77]. It has been reported that silk sericin has antioxidant properties[78-80], good moisturizing effect[78], improved cell attachment[78,81] and enhanced of cell proliferation[76,78]. Silk sericin also shows low immunogenicity[82].

One of the biggest disadvantages of using silk sericin-based polymers is that it causes hypersensitivity reactions.[58,77] A study reported that silk sericin caused type I hypersensitivity reaction and also a delayed hypersensitivity reaction as it increased the production of IgE, causing asthmatic reactions in a few patients.[67,83] Skin prick tests and skin patch tests confirm the same.[83-85] *Escherichia coli* were observed to grow better in agar plates containing silk fibroin than those containing silk sericin.[75] It is also shown that silk sericin does not have anti-bacterial properties.[86]

Mesenchymal Stem Cells-based Method

Mesenchymal stem cells (MSCs) (also called multipotent mesenchymal stromal cells) possess the self-renewal property and can also differentiate into many cell lineages, such as tenocytes, osteoblasts, chondrocytes, adipocytes and myocytes.[87,88] MSCs accelerate wound closure,

enhance re-epithelialization, increase angiogenesis, promote the formation of granulation tissue, modulate inflammation and regulate the remodeling of ECM. This has led to positive effects on wound healing and regeneration of skin (figure 8).[89,90]

A study by Walter et al.[91] demonstrated that MSCs derived from human bone marrow increased the in vitro migration of keratinocytes and fibroblasts which in turn increased the rate of wound closure. Jeon et al.[92] showed that the migratory ability of human skin fibroblasts was elevated significantly when cultured with MSCs derived from human umbilical cord blood.

Studies have also shown that MSCs increase vascular endothelial growth factor (VEGF) which promotes angiogenesis.[93-96] Rat wounds implanted with MSCs derived from rat adipose tissue showed vasculogenesis by the direct differentiation into vascular endothelial cells. MSCs also secreted elevated levels of VEGF and hepatocyte growth factor (HGF)[94]. Various ways in which MSCs enhance wound healing are summarized in **figure 4**.

MSCs have the ability to modulate the inflammatory responses in a manner that favors wound healing. Wounds transplanted with MSCs have shown lower number of inflammatory cells and pro-inflammatory cytokines like interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α).[93]Jeon et al.[92] reported that there was significant increase in the levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx) when fibroblasts were exposed to human umbilical cord MSC-conditioned media.[97]

ECM remodeling enhancing ability has also been exhibited by MSCs.[89,92,98] Media conditioned using human umbilical cord MSCs has been demonstrated to inhibit matrix metalloproteinase (MMP)-1 expression. This suggests that MSCs decrease the degradation of the collagenous matrix. This preserves the matrix and enhances fibroblast regeneration.[92]

A few therapeutic effects of MSCs are tabulated in **table 3** below.

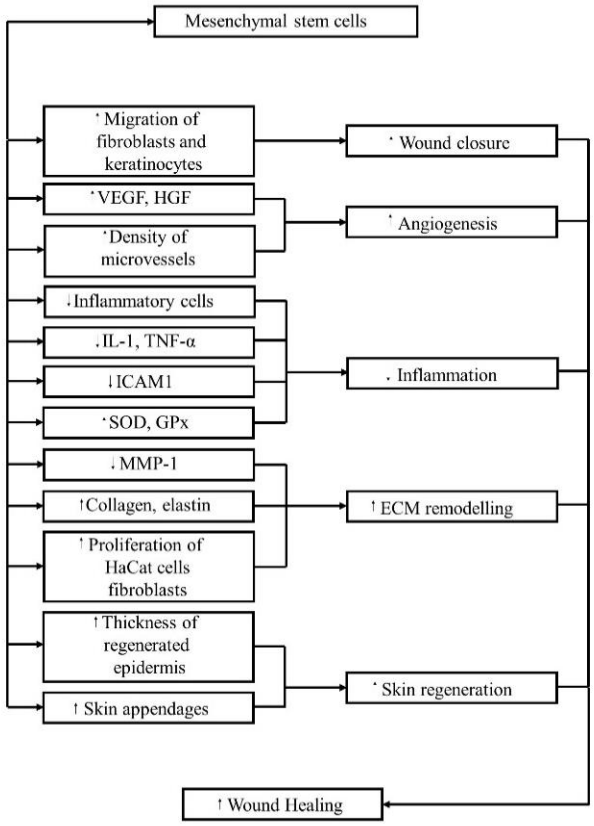

Figure 4: Enhanced Wound Healing by Mesenchymal Stem Cells[87].

(VEGF – Vascular Endothelial Growth Factor, HGF – Hepatocyte Growth Factor, IL-1 – Interleukin-1, TNF-α – Tumor Necrosis Factor-alpha, ICAM1 – Intercellular Adhesion Molecule 1, SOD – Superoxide Dismutase, GPx – Glutathione Peroxidase, MMP-1 – Matrix Metalloproteinase-1, HaCaT – Immortalized Human Keratinocyte)

Table 3: Therapeutic effects of MSCs[87]

Therapeutic Effect	Source of MSC	Wound Healing Model	Reference(s)
Increased Cell Migration	Mouse Bone Marrow Human Amniotic Fluid Mouse	Mouse Human Mouse	99 100 101
Increased Immuno-modulation	Human Gingival Tissue Mouse Bone Marrow Human Bone Marrow	Mouse Mouse Mouse	102 103 104
Increased Angiogenesis	Mouse Bone Marrow Dog Adipose Tissue Mouse Human Adipose Tissue	Mouse Mouse Mouse Mouse	105 106 107 108
Increased Wound Healing Efficacy	Human Amniotic Fluid Human Adipose Tissue Human Bone Marrow	Mouse Mouse Mouse	109 110 111

CONCLUSION

The process of wound healing has been well understood due to the extensive studies performed. Wound treatments or wound care technologies have been improving continuously and the advances in these technologies continue to expand. The use of bioengineered skin substitutes, silk-based biomaterials and mesenchymal stem cells (MSCs) for wound care are a relatively recent technology. Acellular and cellular skin substitutes have been introduced into the market and have shown great results. These come with drawbacks of their own and thus there is scope of improvement in the field of bioengineering skin substitutes. Silk-based biomaterials and MSCs-based wound treatments are still under the scientific research and testing phase and have not been commercialised yet. Both these methods show great promise in accelerating the process of wound healing.

There is a lot of scope for advances in the field of wound care which continues to expand. New technologies and ideas are being proposed frequently to treat wounds better and to accelerate the healing process. The products currently available in the market increase the various techniques and methods that a medical practitioner can use to provide wound treatment based on the type of wound.

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