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A Revolution in Dermatology and Plastic Surgery - Moving to Scarless Healing Through the Application of Regenerative Medicine

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Abstract

Non-healing wounds, burns, and scars from surgical incisions and trauma cost approximately 70 billion dollars annually in the US alone. A number of interventions have been attempted throughout history to facilitate wound healing and skin repair, yet despite these treatments, the healthcare costs and quality of life implications that arise from non-healing wounds, scarring, and skin aging continue to challenge individual patients as well as the healthcare economy. This article describes novel and emerging scientific breakthroughs and technologies to promote healthy wound healing and skin repair using regenerative medicine, the future of scarless wound healing. Topics include: percutaneous wound healing (PCI) to evoke natural cellular regenerative processes, novel transcutaneous drug and molecular delivery systems to apply targeted therapies, new techniques for stem cell identification, isolation, and replication to select for well-functioning and specific cells, and innovative scaffolding to lay the selected cells onto to foster the optimum growth environment and promote scarless healing. In addition, this review will provide an overview of historical attempts at facilitating wound healing, describe the current understanding of the normal and abnormal wound healing process, and discuss existing paradigms for treating abnormal wound healing and skin repair.

Introduction

When insult to the skin occurs, the body must undergo wound healing in order to restore the cutaneous barrier and prevent infection. However, the process of wound healing leads to incomplete regeneration of the original tissue, which results in a new layer that is less tensile, has lost its dermal appendages such as hair follicles and sebaceous glands, and frequently leads to pathological scarring which can cause pain, itching, cosmetically unappealing appearance, and decreased function and mobility [1]. Non-healing wounds, burns, and scars from surgical incisions and trauma cost approximately 70 billion dollars annually in the US alone [2-5]. A number of interventions have been attempted throughout history to facilitate wound healing and skin repair, yet despite these treatments, the healthcare costs and quality of life implications that arise from non-healing wounds, scarring, and skin aging continue to challenge individual patients as well as the healthcare economy. This article describes novel and emerging scientific breakthroughs and technologies to promote healthy wound healing and skin repair using regenerative medicine, the future of scarless wound healing. In addition, this review will provide an overview of historical attempts at facilitating wound healing, the current understanding of the normal and abnormal wound healing process, and existing paradigms for treating abnormal wound healing and skin repair.

Historical Attempts at Facilitating Wound Healing

According to Calabrese et al. [6], early treatments for wound healing typically included "occlusive elastic dressings, saline baths, sulphanilamide powder with tulle grass, silver nitrate, sodium sulphate dressings, glycerin acrifavine dressings in oil, eucol (mixture of chlorine and boric acid), and skin grafting" [6]. The notion that wound healing could be accelerated seems to have been initiated in the early 1900s when researcher Jacob Loeb showed that ionic changes in sea water could induce cell division in sea urchin's eggs. This discovery let future Nobel Prize winner, Alexis Carrel, to investigate chemical and biological agents such as tissue extracts, antiseptics, and alterations of plasma tonicity for their effect on enhancing cutaneous wound repair [6]. From this research sprung further investigations in the 1940s-1960s suggesting that embryo, heart, and skin extracts accelerated wound healing. In 1915, while Carrel was aiding the French military in

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treatment of war wounds, he partnered with British chemist Henry Dakin to create the Carrel-Dakin technique for wound management, which consists of aggressive debridement, delayed wound closured, and Dakin's solution, buffered-hypochlorite solution, administered through rubber tubes deep into the wound [7].

Current Understanding of Natural Wound Healing and Aging Processes

Natural wound healing in response to insult or injury occurs in 3 major phases involving inflammation, proliferation, and maturation (remodeling). Each of these processes is regulated by numerous cytokines that suppress or promote different functions to maintain homeostasis during wound healing, and imbalances may lead to abnormal wound healing, such as chronic wounds or hypertrophic scar formation [6-8]. In addition to injuries or burns, the skin is also subject to aging, a physiologic process comprised of intrinsically genetically predetermined factors and extrinsic environmental and lifestyle factors.

In the first phase of wound healing, the inflammatory phase, hemostasis occurs, vasodilation ensues, growth factors are released, bacteria are phagocytosed, and necrotic material is broken down. Hemostasis occurs *via* platelet aggregation, coagulation, and fibrin deposition. Histamine and serotonin release results in vasodilation Mayet et al. [8]. Phagocytosis and breakdown is predominantly undertaken by macrophages, which are differentiated monocytes that have infiltrated the tissue. Hypoxia inducible factor (HIF-1), a protein released in response to local hypoxia, is essential to the process of macrophage recruitment, bactericidal function, and metabolism, and macrophage-derived reactive oxygen species (ROS) are crucial in activating cytokines and angiogenesis to defend against foreign invaders Ruthenborg et al. [9]. Macrophage-secreted growth factors such as VEGF, platelet-derived growth factor ((PDGF), fibroblast growth factor (FGF), transforming growth factor- (TGF-α), and TGF-β have been reported to be induced by hypoxia Murdoch et al. [10]. PDGF is a chemo attractant for monocytes, macrophages, and neutrophils, and also induces mitosis in fibroblasts and smooth muscle cells *in vitro*. TGF-β induces endothelial cell and fibroblast migration and deposition of extracellular matrix proteins Murdoch et al. [10]. TGF-β exists as subtypes that influence the healing response; TGF-β3 elicits scar-free/regenerative healing response whereas TGF-β1and TGF-β2 elicits fibrotic scarring response. Thus, it has been proposed that in order to mimic the embryonic scar-free profile, therapies should target neutralizing TGF-β1and TGF-β2or adding exogenous TGF-β3.

Two to three weeks after the initial cutaneous insult, the second phase, the proliferative phase, occurs in which granulation tissue is formed and wound contraction and epithelialization transpires through increased activity by fibroblasts, endothelial cells, and keratinocytes. Fibronectin is laid by fibroblasts into a matrix network that determines the structure onto which collagen will be deposited. Type III collagen will be then be laid down and later converted to type I collagen [11]. The result of this the production of new capillaries and a bed of collagen that pulls wound edges together *via* contraction *via* myofibroblasts.

During the final maturation phase, three weeks to two years after the original injury, scar tissue is remodeled *via* collagen synthesis and breakdown [7]. Collagen molecules are modified and form triple helical structures which are then cross-linked for strength and stability, and apoptosis occurs to remove unnecessary cells [12,8]. Vitamins A and C are used in the production of collagen and lead to the proliferation and differentiation of epidermal and dermal cells, and they also help maintain homeostasis between collagenolysis and collagenesis [11,13]. Vitamin A may also support the release of TGF-β3 over the more pro-fibrosis inducing TGF-β1 and TGF-β2 molecules and create a more lattice-patterned network [14].

Characteristics of skin aging included the development of fine wrinkles, skin thinning, and increased laxity of the skin [15] which can caused by intrinsic and extrinsic factors. Intrinsic skin aging is caused by accumulated damage to DNA due to oxidative damage that occurs through cellular metabolism [16]. Extrinsic aging is can be caused by UV light, pollution, smoking, alcohol and diet and can lead to DNA mutations and protein aging modifications that lead to increased degradation of collagen, abnormal elastin, and loss of glycosaminoglycans (GAGs), which are responsible for the integrity and hydration of the skin [17].

Non-Regenerative Paradigm for Accelerating Wound Healing

A number of non-regenerative techniques are currently being implemented to accelerate wound healing and promote skin vitality. Debridement plays an important role in wound healing to prevent devitalized, necrotic tissue from increasing risk of infection and/or interfering with re-epithelization and contraction Mayet et al. [8]. Maintaining a moist wound/dressing environment is also crucial to helpingrecruit cellular host defenses and maintaining an optimal, hydrating milieu for wound healing to proceed Mayet et al. [8]. Treatment methods such as hyperbaric oxygen and local oxygen therapy are currently used for recalcitrant wounds based on the understanding that improved wound oxygenation is important for cell proliferation, immune response, angiogenesis, collagen synthesis, and epithelialization [18]. Other therapies to treat burns, wounds, and skin aging include operative techniques such as scar revision surgeries (z-plasties), tissue transfers and grafts, and non-operative techniques such as injections and ablative and non-ablative procedures [14]. Flaps, grafts, and surgical revisions of burns or scars can help to camouflage scars but can never truly erase them. In addition, they often require multiple surgeries and the pose the risk associated with surgery such as of blood loss, infection, and adverse events related to anesthesia [19]. Skin injections used to treat scarring include steroid injections to flatten scars and reduce symptoms, and collagen and fat filler injections for depressed scars [19]. The disadvantage of injections is the potential for contour irregularities, and results may be influenced by the skill of the provider [19]. Ablative and non-ablative procedures include CO_2 laser resurfacing, deep chemical peels, dermal abrasion, fractionated laser, radiofrequency heat, superficial repetitive peels and intense pulsed light (IPL). In general, ablative therapies cause vaporization of the epidermis and possibly the dermis, and non-ablative therapies cause controlled over heating of the tissues, both of which incite new collagen formation and dermal remodeling, which results in tissue tightening and softer, flatter scars [19,20]. The downfall of these methods is that these procedures injure or destroy the epidermis and basement membrane, which leads to dermal papillary fibrosis (cicatrisation) and increased risk of photo damage and post-inflammatory hyper pigmentation [14], as well as possible reactivation of latent herpes [19].

The Future of Wound Healing

Ideal wound healing should achieve complete restoration of the

skin structure and functions with minimal to no scarring over a short period of time with minimal discomfort to the patient. Regenerative healing uses cell-based therapies to promote scarless wound healing by replacing, engineering, or regenerating human cells, tissues, or organs. Theoretically, the regenerative approach could revolutionize wound healing by providing an adequate microenvironment and carefully selected cells to replace missing components in injured tissue in order to modulate inflammation, release growth factors, and stimulate native cell populations to heal. One method that has been proposed to induce regeneration within the tissue is called percutaneous wound induction (PCI), which was introduced in 1997 and uses multiple needle application to treat scars and wrinkles [14]. PCI is a technique of rolling tiny needles in multiple directions to generate thousands of micro wounds in the dermis, thereby resulting in a natural, confluent, superficial post-traumatic dermal inflammation that employs the normal inflammatory wound cascade, without the risk of dyspigmentation [14,11,13,21]. Because PCI works by creating narrow clefts in the epidermis and stratum corneum, the epidermis is left intact with no dermabrasive reduction in epidermal thickness (as opposed to ablative techniques), and it minimizes exposures to stressors such as air, infection, and mechanical tension. In addition, studies have shown that PCIin combination with topical vitamins has led to greater epidermal thickness Aust et al. [13], up-regulation of TGF-β3, increased thickened and more loosely woven collagen, and enhanced production of GAGs and growth factors [14,13,21]. The disadvantage of PCI is that there may be significant swelling afterwards, and the final result takes long than laser resurfacing [14].

Other regenerative techniques involve correcting extrinsic defects that lead to abnormal skin healing, by delivering molecular therapies directly to the wound. For example, deferoxamine (DFO) is an iron chelator that increases HIF-1α activity by preventing iron-induced reactive oxygen species and subsequent oxidative stress. It can be delivered in a trans delivery system or "patch" to help prevent ulcerations and accelerate healing in chronic wounds Duscher et al. [22]. Novel drug delivery systems have been designed such as microspheres, nanoparticles, liposomes, sponges and wafer, and nano and microemulsions to provide controlled, targeted delivery of drugs to wounds while creating an optimum environment for healing [23]. Smart polymeric delivery materials that initiate and foster cellular processes for healthy wound healing are promising for skin regeneration.

Previous cell-based therapies have not been as successful as they could be because cells have been isolated and manufactured based on surface markers in the literature, without basis for their intracellular function. New technologies use bioinformatics processing of single cell transcriptional data and microfluidics platforms to identify, isolate, and quality test the specific cells based on how they function. Specifically, single cells from adipose and bone marrow undergo transcriptional analysis and are probed for 96 genes involved in tissue repair, so that the most favorable are selected for wound healing and the surface markers that match those cells can be isolated [24-26]. In doing so, cells that promote normal, healthy healing can be isolated and replicated over those of that may be more prone to fibrosis and scarring.

Finally, novel scaffolding to lay the selected cells onto can enhance growth factor production, increase survival of delivery cells, and promote scarless healing. One such scaffolding employs a biomimetic regenerative extracellular matrix component (pullulan-collagen) that is present during scarless embryonic healing to create a hydrogel dressing [27-29]. This skeleton framework can then be layered to mimic the normal layers of the skin, so that each layer has cell properties and surrounding milieu that is unique to the stratification of normal skin.

Conclusion

Wound healing is a complex and intricate process that requires carefully orchestrated series of events to achieve homeostasis and healthy wound healing. Any shift in the amount or types of growth factors, healing environment, or cell expression can lead to under-healing (chronic wounds) or over-healing (scarring, keloids, hypertrophic scars). The consequences of these effects result in unfavorable cosmetic results and decreased quality of life as well as increased morbidity and mortality causing significant healthcare expenditures. Traditional methods to accelerate or improve wound healing have attempted various techniques ranging from antiseptics, topical applications, and dressings to surgical techniques and lasers. However, ideal wound healing has yet to be achieved. Regenerative medicine will revolutionize the future of wound healing by using individualized stem-cell based therapies to laminate highly specialized cells onto novel biomimetic frameworks can be used to "recreate" injured tissue. Furthermore, novel molecular drug delivery systems can allow for more directed, targeted therapies to promote wound healing, and methods such as percutaneous collagen induction can stimulate natural wound healing processes.

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