The Use of Biologic Scaffolds in the Treatment of Chronic Nonhealing Wounds

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Significance: Injuries to the skin as a result of illness or injury, particularly chronic nonhealing wounds, present a major healthcare problem. Traditional wound care approaches attempt to control the underlying causes, such as infection and ischemia, while the application of wound dressings aims to modify a poorly healing wound environment into a microenvironment more closely resembling an acute wound allowing the body to heal the wound naturally.

Recent Advances: Regenerative medicine approaches, such as the use of biologic scaffold materials comprising an intact extracellular matrix (ECM) or individual components of the ECM, are providing new therapeutic options that focus upon the provision of biochemical cues that alter the wound microenvironment to facilitate rapid restoration of normal skin architecture.

Critical Issues: The incidence of chronic nonhealing wounds continues to increase. For example, between 15% and 20% of diabetics are likely to develop chronic, nonhealing foot wounds creating an increasing burden on healthcare systems worldwide.

Future Directions: Developing a thorough understanding of wound microenvironment and the mechanisms by which biologic scaffolds work *in vivo* has the potential to markedly improve outcomes in the clinical translation for the treatment of chronic wounds.

SCOPE AND SIGNIFICANCE

THE USE OF BIOLOGIC SCAFFOLD materials for a variety of applications has increased dramatically during the past two decades. These scaffolds include those comprising an intact extracellular matrix (ECM) or individual components of the ECM, and those comprising hybrids incorporating a synthetic component with a biologic component.

The mechanisms by which such scaffolds support and promote structural and functional remodeling of injured tissues *in vivo* are being increasingly understood. The scaffold remodeling process has been described as constructive remodeling, which represents the scenario in which site-appropriate organized tissue with at least some degree of functionality is deposited at the site of scaffold placement. This outcome is in contrast to the default tissue healing response, which would be characterized by scar tissue and general lack of functionality. Each anatomic site and clinical application has distinctive characteristics and the use of biologic scaffolds in these different locations has shown various degrees of success.

Chronic nonhealing wounds are commonly associated with comorbidity characteristics, such as obesity, diabetes, and malnutrition. The success/failure of biologic scaffolds in treating

chronic wounds will depend upon a thorough understanding of the mechanisms by which these materials work *in vivo*, but the potential to markedly improve outcomes in the clinical translation for the treatment of chronic wounds is noteworthy.

TRANSLATIONAL RELEVANCE

The outer layer of the skin (epidermis) can regenerate, but injuries that breach the subjacent dermis relegate healing to granulation and scar tissue formation. Biologic scaffolds can transform the default scar tissue response toward one that includes components of true regeneration. This modulation of default healing has been termed as constructive remodeling. A biologic scaffold approach can have direct translational relevance to full thickness, and difficult to heal skin wounds.

CLINICAL RELEVANCE

In contrast to most wound dressings designed to protect the wound surface and maintain various states of hydration, biologic scaffold materials function as an inductive microenvironment. Mechanisms by which these ECM-based scaffold materials function in soft tissue locations, such as skeletal muscle, tendons, and the gastrointestinal tract, include relatively rapid degradation, which releases embedded cytokines and chemokines, generation of bioactive cryptic peptides with a variety of constructive wound healing properties, modulation of the innate immune response, and recruitment of endogenous stem/progenitor cells to the site of scaffold remodeling. The extent to which these processes occur in the setting of chronic skin wounds with concomitant systemic pathology, such as diabetes, peripheral vascular disease, and malnutrition, has been largely unexplored. The clinical relevance of these biologic scaffolds is predicated upon these scaffold-mediated inductive processes. The potential to change the default healing response may shorten the time to complete healing, prevent advancement of these wounds to deeper structures, and result in improved cosmetic outcomes.

OVERVIEW

Injuries to the skin as a result of illness or injury present a major healthcare problem. The incidence of chronic nonhealing wounds, such as venous or diabetic ulcers, continues to increase. Wound management has traditionally involved controlling the underlying causes, such as infection, ischemia, or diabetes, and allowing the body to heal the wound

naturally. Regenerative medicine approaches, such as the use of biologic scaffold materials comprising an intact ECM or individual components of the ECM, provide additional therapeutic options. These regenerative medicine approaches focus upon the provision of biochemical cues that alter the wound microenvironment to facilitate rapid restoration of normal skin architecture. The present article describes the various types of scaffold materials available, the mechanisms by which constructive remodeling occurs, and potential future directions.

DISCUSSION
Nonhealing wound microenvironment

Injuries to the skin as a result of illness or injury present a major healthcare problem. Approximately, 12 million wounds will be treated in emergency departments in the United States annually,[1] and more than 2 million people will suffer from pressure ulcers.[2] Furthermore, the incidence of chronic nonhealing wounds, such as venous or diabetic ulcers, continues to increase. In 2007, in the United States alone, 23.6 million people were diagnosed with diabetes,[3] of which between 15% and 20% are likely to develop chronic, nonhealing foot wounds.[4] Wound management has traditionally involved controlling the underlying cause, such as infection, ischemia, or diabetes, and allowing the body to heal the wound naturally. Regenerative medicine provides additional therapeutic options, which focus upon the provision of biochemical cues that alter the wound microenvironment to facilitate rapid restoration of normal skin architecture.

The wound repair process is highly complex, requiring the activation and synchronization of multiple biological pathways if tissue integrity and hemostasis are to be restored. Activation of these biological pathways gives rise to a dynamic wound microenvironment that consists of cells and the ECM and a complex milieu of enzymes, growth factors, and cytokines. In healthy individuals, the response to injury occurs in a series of overlapping, but distinct stages of hemostasis, inflammation, new tissue formation, and tissue remodeling.[5] Hemostasis and inflammation occur immediately following tissue injury. Platelets initiate the wound healing process through the activation of the coagulation cascade and the release of proinflammatory mediators, including platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), fibroblast growth factor (FGF), and insulin-like growth factor-1 (IGF-1), among others.[2,6] Polymorphonuclear leukocytes migrate to the wound site in response to these secreted factors,

followed by macrophages that engulf and attempt to destroy any microbes and necrotic debris. Macrophages play a critical role in the wound healing process by releasing proteases, which degrade damaged ECM as well as a host of proinflammatory and tissue remodeling cytokines.[7]

Concurrent with the inflammatory response is the commencement of new tissue formation, which is characterized by the migration and proliferation of keratinocytes over the injured dermis and a robust angiogenic response. Fibroblasts begin to replace the fibrin matrix and necrotic tissue of the wound with new ECM initiating the formation of granulation tissue. Some fibroblasts will differentiate into contractile myofibroblasts, which contribute to wound contraction. Key regulators of these processes include hepatocyte growth factor (HGF), FGF-2, -7, and -10, TGFα, and vascular endothelial growth factor A (VEGF-A).

The remodeling phase of wound repair involves maturation of the ECM and restoration of the wound microenvironment toward that of normal skin; a process that may take up to 12 months to complete. However, even in healthy individuals, sebaceous glands, hair follicles, sweat glands, and sensory nerves typically fail to form and wounds that include the full thickness of the dermis never regain the properties of uninjured skin, remaining as dense, fibrous scar tissue.

Chronic wounds are defined as wounds that fail to proceed through the normal healing response or fail to produce functional integrity within 3 months. As such, all wounds have the potential to become chronic, although the most common forms of chronic wounds are venous, arterial or diabetic ulcers, and pressure sores.[8,9] In these chronic nonhealing wounds, the wound microenvironment is fundamentally altered. The complex interplay of growth factors and cytokines becomes disrupted and the normal phases of wound healing cannot be completed. Figure 1 demonstrates the key differences between the normal wound healing environment and that of a chronic nonhealing wound. Of particular significance in nonhealing wounds are the reduction in angiogenesis, decrease in growth factors, increased incidence of infection, and the increase in the severity and duration of inflammation characterized by a self-sustaining proinflammatory (M1) response. The presence of increased amounts of proteolytic enzymes within chronic wound sites also contributes to delayed healing. These proteolytic enzymes, called matrix metalloproteinases (MMPs), are capable of degrading most of the components of the ECM. In chronic wounds, the increased levels of MMPs degrade and inhibit the deposition of new ECM, which in turn inhibits cell migration. MMPs are also capable of degrading the growth factors and cytokines that regulate the wound microenvironment, further limiting the progression of wound healing.[10]

Growth factors and cytokines help regulate the wound healing process through a series of complex feedback mechanisms. In chronic wounds, this
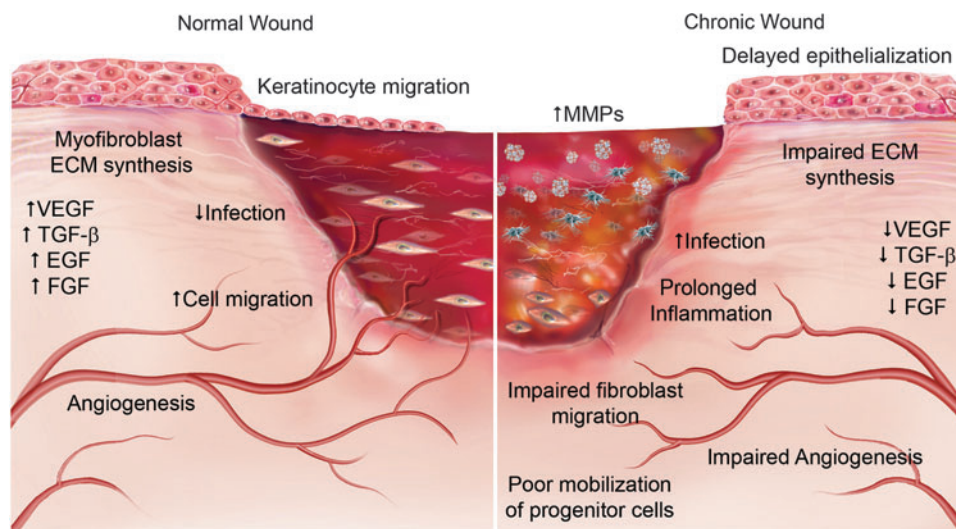
Figure 1. The key differences between the normal wound healing environment and that of a chronic nonhealing wound. Chronic wounds are characterized by prolonged inflammation and infection with delayed epithelialization and impaired fibroblast migration and extracellular matrix (ECM) synthesis. There is increased matrix metalloproteinase (MMP) activity and a decrease in growth factor expression leading to impaired angiogenesis and poor mobilization of circulating progenitor cells. Arrows indicate increase (↑) or decrease (↓). EGF, epidermal growth factor; FGF, fibroblast growth factor; TGFb, transforming growth factor; VEGF, vascular endothelial growth factor. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

growth factor and cytokine milieu is polarized toward inflammation, including increased amounts of interleukin 1α (IL-1α), IL-1β, and tumor necrosis factor α.[2,10,11] Many of these cytokines affect the deposition of new ECM either by decreasing the synthesis of ECM molecules or stimulating the synthesis of MMPs. Similarly, decreases in the expression of TGFβ1, IGF-1, VEGF, and PDGF-BB have been shown to correlate with decreased angiogenesis and delayed wound healing in diabetic and venous ulcers.[12] Management of these chronic wounds has traditionally required a lengthy complex approach that addresses both the pathophysiological causes, such as debridement of devitalized tissue and infection control, as well as systemic factors such as compromised nutrition and venous insufficiency.

Current treatment of nonhealing wounds

Current best practice for the treatment of dermal wounds depends upon the type of injury. If the wound is larger than 4 cm in diameter, skin grafting may be performed. Tissue flaps can also be used, but must obviously be taken from sites adjacent to or near the wound to minimize differences in skin pigment and composition between the donor and recipient sites. While skin grafting and tissue flaps can be used to treat large, chronic nonhealing wounds, these wounds are typically treated with a more conservative approach with the objective of protecting the wound and preventing desiccation and infection at the wound site, thus allowing the natural healing process to proceed.

Current standard of care for nonhealing wounds attempts to address key elements of impaired wound healing (Fig. 2). The Wound Healing Society has promoted the use of the acronym T.I.M.E. to refer to these wound healing steps. T stands for tissue and the assessment of the wound site and its defects such as devitalized or necrotic tissue. I refers to the presence of inflammation, infection, or both. M refers to the moisture balance in the wound. E describes the wound edge and the extent of reepithelialization.[13] Thus, the first stage in the treatment of any chronic wound involves debridement of the wound site to remove devascularized material, necrotic tissue, and infectious debris. Successful debridement preserves vital tissue and can convert a poorly healing wound environment into a microenvironment more closely resembling an acute wound. In addition, there is increasing evidence to support the use of negative pressure therapy following debridement. This use of negative pressure (i.e., wound VAC) reduces fluid around the wound while promoting granulation tissue formation.[14]
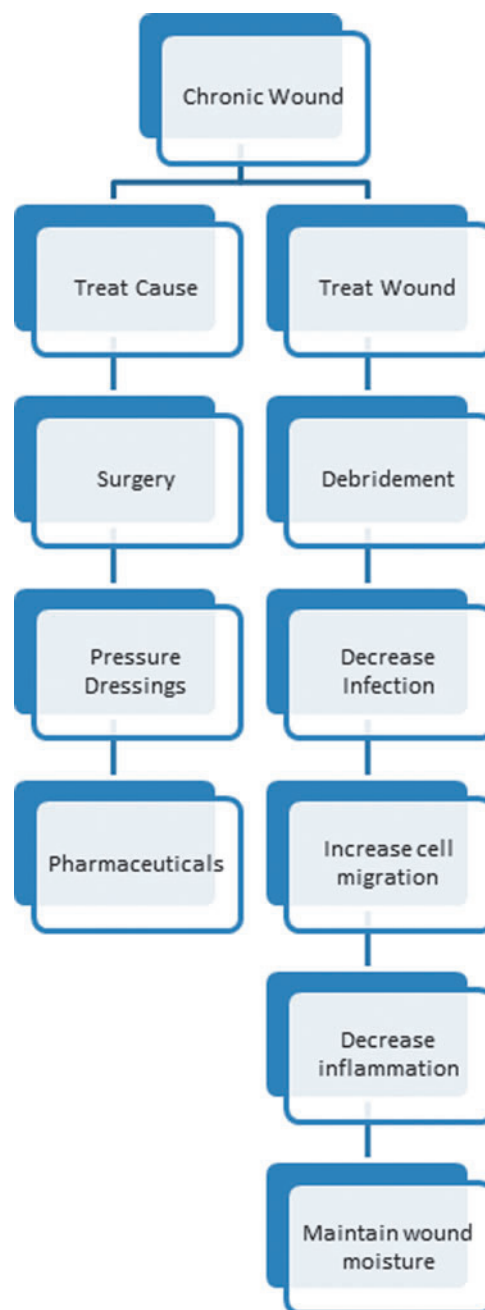
Figure 2. Diagram showing the current approaches to wound care. Current treatment options include treating the cause such as improving circulation or treating the wound directly by controlling infection and inflammation to promote healing. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

Control of inflammation and infection are equally important to successful wound healing. The presence of β-hemolytic streptococci or a concentration of bacteria, such as *staphylococcus aureus*, above 10^5 colony-forming units per gram of tissue is known to impair healing.[15] Ultimately, current successful treatment for chronic wounds depends upon the application of an appropriate

wound dressing. Choice of wound dressing depends on the stage of wound healing and aims to maintain a moist wound environment while minimizing friction to protect the periulcer skin. These wound dressings range from the relatively simple, such as paraffin gauze, to complex hydrogels and colloids that may or may not contain bioactive factors to promote angiogenesis or reepithelialization. For venous and diabetic ulcers, graduated compression bandages are also used to reduce edema and improve venous return. While hydrogels, foams, and hydrocolloids have been developed in recent years, data suggest that traditional therapies such as saline or paraffin gauze dressings and graduated compression bandages are just as effective. As a result, chronic wounds are still associated with a long recovery period and significant patient morbidity.[16] During the last 30 years, advances in cell culture techniques together with a greater understanding of the wound healing process and the factors that constitute the wound microenvironment have led to the development of a number of biologic dressings for wound repair. These biologic materials attempt to restore the wound microenvironment by providing either bioactive factors and ECM components or both to stimulate granulation tissue formation, angiogenesis, and reepithelialization.
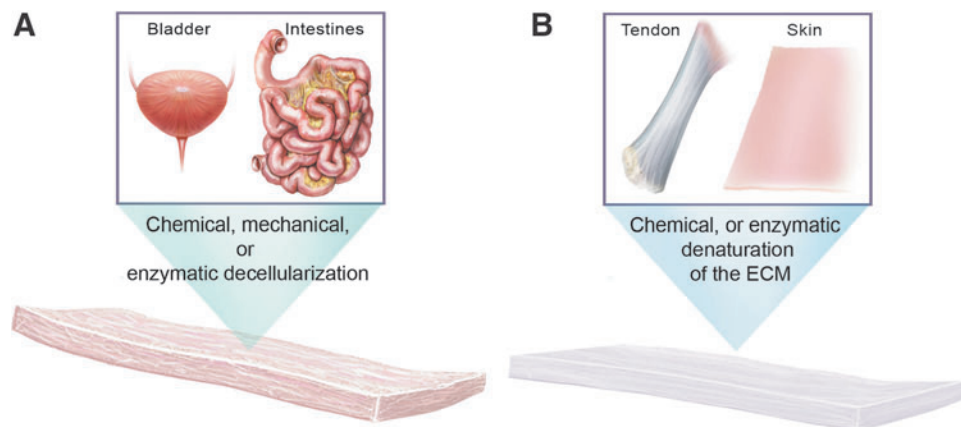
Overview of biologic scaffolds

Biologic scaffold materials comprise the ECM or individual components of the ECM, such as collagen, laminin, or hyaluronan (Fig. 3). The ECM represents the secreted products of resident cells within each tissue and organ. These molecular components are arranged in tissue-specific patterns, which are responsive to and optimized for the physiologic and biomechanical requirements of each tissue.[17] The three-dimensional ultrastructure of the matrix, including the ligand landscape, available to cells that encounter the ECM is extraordinarily complex. Attempts to synthetically manufacture mimics of the ECM would logically require a comprehensive understanding of both the organization and composition of the matrix at the ultrastructural level. Since such an understanding does not exist, by definition it is not possible to create faithful mimics of the ECM.

The biologic properties of the matrix, which affect the interaction with resident cells and infiltrating cells, are partially understood. The matrix acts as an orchestrator of cell behavior, including modulation of macrophage phenotype, proliferation, mobilization, differentiation of stem and progenitor cells, and regulation of angiogenesis, among others.[18–21] These biologic properties can be retained in biologic scaffolds that are prepared by methods that preserve the composition and structure of the matrix. Stated differently, the methods of manufacturing a biologic scaffold material for therapeutic use play a critical, if not defining role, in the clinical outcomes.

Biologic scaffolds manufactured for the treatment of nonhealing wounds are typically designed to degrade. The degradation process of these scaffolds is particularly important for the release of embedded signaling molecules and the generation of cryptic peptide molecules by enzymatic cleavage of parent molecules, such as collagen and laminin. These bioactive cryptic peptides play a key role in the observed biological activity of these materials.[22,23] The following section provides more detail regarding the mechanisms by which biologic scaf-

Figure 3. Preparation of biologic scaffolds. Biologic scaffolds can be prepared either by the decellularization of tissues and organs **(A)** or by degrading the ECM and isolating and purifying individual ECM components **(B)**. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

folds support constructive remodeling processes, especially in the context of the integumentary system.

Use of biologic scaffolds in wound repair

At its simplest, the objective of all wound repair approaches is to create an environment that minimizes infection, promotes the correct moisture balance, and facilitates reepithelialization of the wound. Although a comprehensive understanding of the microenvironmental conditions that exist within mammalian tissue in both healthy and injured tissue is still lacking, the convergence of recent findings in the field of stem cell biology and regenerative medicine has highlighted the importance of the ECM in providing such a friendly microenvironment and regulating cell behavior and promoting tissue repair (Fig. 4). The recognition of the importance of the ECM in wound healing has led to the development of numerous wound healing products derived from mammalian ECM. These products may be biologic and derived from animal or human tissues or they could be composites containing a combination of biologic and synthetic products. For the purpose of this review, the term biologic scaffold will refer to all ECM-based materials and engineered ECM scaffolds will refer to materials produced *ex vivo* from individual ECM components with or without synthetic components. At least five different ECM components have been identified as important mediators of wound healing: (1) structural proteins such as collagen and elastin, (2) glycoproteins such as fibronectin and laminin, (3) glycosaminoglycans (GAGs), (4) proteoglycans, and (5) matricellular peptides. Engineered ECM scaffolds have been fabricated from each of these individual components.

Engineered ECM scaffolds, to date, include natural materials, such as collagen, fibronectin, and hyaluronan, with and without synthetic materials, such as polyglycolic acid, polylactic acid, nylon, and silicone.[24] Collagen is perhaps the most widely used ECM component in wound dressings and scaffolds.[25] Products, such as Puracol Plus® (Medline Industries), Fibracol Plus® (Systagenix) or BIOPAD® (Angelini Pharma), are designed as topical wound dressings. These dressings comprising a microfibrous type I collagen sponge are perhaps the simplest biologic scaffold and primarily function to absorb wound exudate and prevent desiccation of the wound rather than provide any bioactive component. The benefit of these materials over standard wound dressings is that as the scaffold absorbs liquid the collagen forms a hydrogel, which protects the wound. The collagen also sequesters MMPs from the wound environment, preventing further wound breakdown. However, they are typically replaced after only a few days, and so do not function as a typical scaffold to direct tissue repair. Attempts have been made to use collagen in combination with a GAG matrix, which showed the ability to regenerate injured dermis.[26] However, it has been suggested that a construct composed entirely of type I collagen may not be
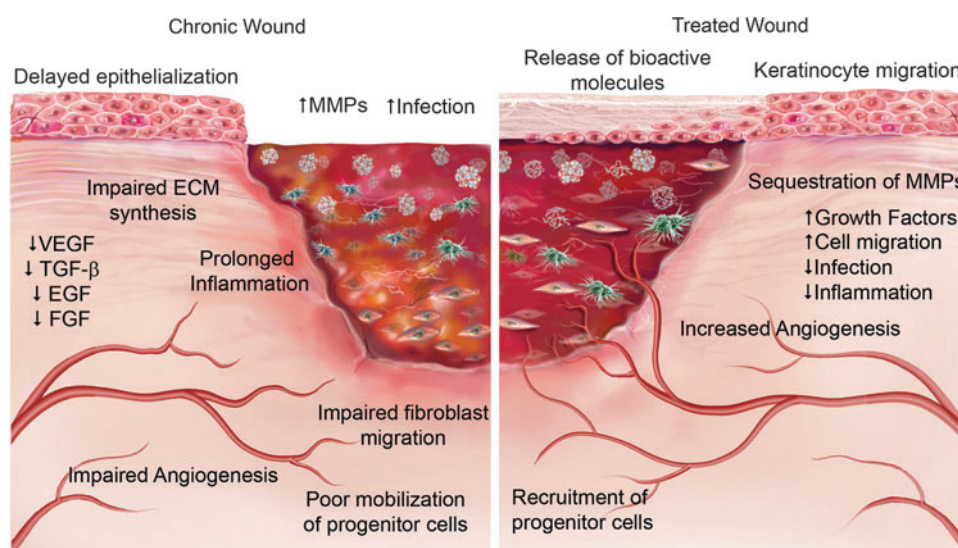
Figure 4. Comparison of a chronic wound and one treated with a biologic scaffold highlighting the importance of the ECM in providing a friendly microenvironment and regulating cell behavior. As the biologic scaffold is degraded, it releases bioactive ECM fragments that sequester MMPs, decrease inflammation, and promote increased cell migration and angiogenesis. Arrows indicate increase (↑) or decrease (↓). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/wound

optimal to promote regeneration.[6,27] Similarly, hydrogel dressings, such as Tegagel™ (3M) and Vigilon® (CR Bard), have become common treatments for wound care. These hydrogels can be manufactured from biologic materials, such as alginate, or synthetic materials such as polyethylene oxide. Few bioactive hydrogels that actively promote wound healing have made it to market. One example is Xelma® (Mölnlycke Health Care), which consists of amelogenin peptides within a polyethylene glycol–alginate gel.[28] Amelogenin proteins have been shown to stimulate growth factor release and proliferation of fibroblasts, and Xelma been shown to significantly reduce the size of venous ulcers.[29,30]

Integra™ (Integra Life Sciences)[31] is a composite of cross-linked bovine collagen and chondroitin 6-sulfate isolated from shark skin, with a silicone covering. The silicone covering is semipermeable, controlling water vapor loss from the wound and providing structural strength to the graft. After placement on the wound, the collagen and chondroitin matrix recruits dermal fibroblasts to the wound, which then secrete new ECM to restore the dermal bed. The graft matrix degrades in ∼2–3 weeks leaving only the silicone covering. The silicone sheet can then be removed. A related product is Biobrane® (Smith & Nephew), which consists of a silicone sheet with a partially embedded nylon fabric embedded on the surface.[32] This nylon fabric is then coated with porcine dermal collagen. Blood and sera from the wound form a clot within the nylon fabric attaching the dressing to the wound, while the collagen promotes fibroblast growth and maintains a hydrated environment. This product has been targeted toward healing donor skin graft sites and skin slough disorders,[33,34] but has been shown to promote granulation tissue in hard-to-heal lower extremity wounds.[35]

Wound dressings based on natural ECM materials derived from decellularized tissues share a number of similarities in their mode of action in promoting wound healing; however, as described previously, these products differ greatly in their source material and preparation and processing.[36] Although well-designed and informative studies have been conducted on a variety of decellularized tissues, perhaps the most comprehensively studied matrices regarding biological activity, composition, mechanical properties, and macro- and ultra-structure are those derived from the porcine small intestinal submucosa (SIS)[19,37–45] and from the porcine urinary bladder matrix (UBM).[46–53] By dry weight, SIS-ECM comprises more than 90% collagen with the majority of that being type I collagen.

Small amounts of type III, IV, V, and VI collagens are also present,[54] as are adhesive proteins such as fibronectin and laminin.[38,55] Natural ECM scaffolds also contain a variety of GAGs, including heparin, heparan sulfate, chondroitin sulfate, and hyaluronic acid.[41] The amount of these GAGs remaining in the tissue following decellularization depends greatly on the methods of decellularization, especially those methods, which use ionic detergents known to remove GAGs from the ECM.[36] Various growth factors have been identified within these biologic matrices, even following dehydration and terminal sterilization. These growth factors include TGFβ,[56] basic FGF,[57] and VEGF.[58] In addition, cryptic peptides released by the ECM degradation process have been shown to initiate and sustain the recruitment of bone marrow-derived cells, which actively participate in long-term tissue remodeling.[21,59,60]

Oasis® Wound Matrix (Healthpoint) is an SIS-ECM graft consisting of noncross-linked porcine SIS-ECM. Oasis has been shown to significantly reduce healing times in full-thickness venous ulcers[61] and has also been shown to be effective as an alternative to split-thickness skin grafting.[62] The added benefit of Oasis is that multiple treatments can be performed without removal of previous Oasis dressings due to the very rapid degradation of the SIS material. *In vitro*, SIS-ECM has been shown to support epithelial cell differentiation and formation of a new basement membrane.[42] Studies utilizing SIS-ECM for the treatment of tissues other than skin have shown that this material also supports angiogenesis, neurogenesis, and the repopulation of the wound site with multiple tissue-specific cell types primarily through the migration of tissue resident and circulating progenitor cells.[54,63–67]

Matristem® is a natural ECM scaffold consisting of noncross-linked porcine UBM-ECM. The primary advantage of UBM-ECM over other natural ECM products is that UBM-ECM retains the basement membrane component of the urinary bladder on one surface of the biologic scaffold. The basement membrane functions to anchor epithelial tissues to the ECM in organs such as the skin and blood vessels. Basement membrane proteins are also potent promoters of angiogenesis, and so retention of the basement membrane has been suggested to be advantageous in enhancing tissue repair and wound healing. Matristem has been extensively studied as a wound dressing for venous, diabetic, and ischemic ulcers. Lecheminant and Field performed a retrospective study on the use of Matristem and found that application of the product significantly reduced healing time from an

average of 25.5–9.8 weeks, although their study also highlighted a number of risk factors that should be considered and addressed to maximize the effectiveness of the Matristem product.[52] Other case reports have described similar successful applications for other hard-to-heal wounds, such as radiation wounds,[68] open pilonidal wounds,[69] and chronic wounds, in patients with a mixed etiology, including diabetes, hypertension, and peripheral vascular disease.[70]

Primatrix™ (TEI Biosciences) is a noncross-linked ECM derived from decellularized fetal bovine dermis intended for the treatment of nonhealing ulcers, second-degree burns, and surgical wounds. The product is distinctive, in that it utilizes a fetal tissue that is rich in type III collagen, which is the first type of collagen synthesized during both embryonic development and wound healing.[71,72] The fetal bovine dermis ECM in Primatrix is ~30% type III collagen.[73] In addition to providing elasticity to the ECM, type III collagen has been shown to promote migration of fibroblasts[74] and to be an essential regulator of ECM deposition and organization.[75,76] Primatrix becomes incorporated into the wound and rapidly degrades and has shown success for the treatment of acute full-thickness wounds.[77]

Alloderm® (Lifecell), GraftJacket® (Wright Medical Technology), and DermaMatrix™ (Synthes) are decellularized dermal constructs derived from human dermis. GraftJacket is chemically cross-linked to maintain the collagen architecture, while Alloderm and DermaMatrix are noncross-linked. Unlike xenogeneic ECM scaffolds, constructs derived from human tissue are classified as tissue transplants rather than surgical mesh devices (i.e., medical devices) and therefore are not regulated by the FDA. As a result, there are fewer restrictions on the applications for which these devices can be used. However, since these materials are derived from human tissue, careful screening is required to ensure that the source tissue is free from transmissible pathogens, such as Hepatitis B and C viruses, HIV, and syphilis. Clinically, these products have been indicated for the treatment of nonhealing non-ischemic ulcers and other dermal wounds and have shown the ability to significantly reduce healing time, wound volume, and depth.[78] GraftJacket increased the probability of successful wound healing of diabetic foot ulcers within 12 weeks by 2.7-fold with a significant increase in the total number of successfully healed wounds.[79]

The use of biologic therapies for wound repair has shown notable advantages over traditional therapies in terms of the quality of the remodeled tissue and speed of repair. However, ease of handling, cost, and shelf life are of concern. It is clear that over the last 30 years the need for optimal wound care and the concept of moist interactive wound dressings have been recognized. However, the complexities of different wound environments, coupled with the plethora of biologic materials that differ by source, method, or preparation, and method of sterilization, have created a complex range of products, which although similar in nature vary greatly in their ability to promote tissue regeneration. Although clinical studies have been generally positive, results have been mixed, and today, 50% of all wounds still do not receive appropriate care. Biologic wound dressings, when used appropriately, have the potential to change the default wound healing response, but the full ability of these materials to promote constructive remodeling will not be realized until a comprehensive understanding of the biology of the ECM and wound microenvironment is acquired.

FUTURE DIRECTIONS

The development of bioactive wound dressings has increased in recent years, in part, due to increased research on wound dressings to treat the complex extremity injuries suffered as a consequence of modern warfare. Increasing focus is being placed on the development of a multifunctional device that can promote rapid wound healing and does not need to be replaced. These multifunctional devices may include the ability to control hemostasis, deliver local analgesia or infection control for extended periods, regulate the inflammatory response, and stimulate the reconstruction of functional site-appropriate tissue.

Scar-free healing is a primary goal in developing new wound healing strategies. While embryonic skin has the ability to repair without scarring, adult skin does not have this ability due, in part, to the immune response and inflammatory cascade. TGFβ1–3 and PDGF seem to play prominent roles. It has been proposed that scar-free healing can be achieved through the addition of TGFβ3.[80–82] However, while TGFβ3-mediated healing has been successfully demonstrated in rodents, pigs, and healthy human volunteers, phase III clinical trials failed to show any significant improvements and primary and secondary end points were not met.[83] Other groups have investigated the use of other growth factors, including epithelial growth factor[84] and FGF,[85] for the treatment of chronic nonhealing wounds. Studies using PDGF have shown significant improvements in healing of chronic ulcers in the clinical trial.[86]

Control of hemostasis and wound hydration has led to the investigation of chitosan as a wound dressing for nonhealing wounds.[87–90] The benefit of these scaffolds is their ability to rapidly control hemostasis while also modulating the wound environment to maintain an optimal hydration level and prevent desiccation. Furthermore, these chitosan materials can be combined with other bioactive molecules to provide combination dressings that promote wound healing while also combatting infection[87] or modulating inflammation.[88] The potential for other hydrogel materials to promote wound healing while delivering bioactive factors, such as antibiotics,[91] or to deliver analgesia to the wound site for prolonged periods[92] are also being investigated. However, it is likely that the greater advances in wound healing will come as a result of studies that characterize the wound microenvironment and elucidate the molecular and biochemical pathways involved in the regulation of adult wound healing versus regeneration.[11,93,94]

SUMMARY

In contrast to most wound dressings designed to protect the wound surface and maintain various states of hydration, biologic scaffold materials function as an inductive microenvironment. The constructive remodeling of biologic scaffolds represents a scenario in which site-appropriate organized tissue forms at the site of scaffold placement and offers new therapeutic options for the treatment of chronic nonhealing wounds. By altering the wound microenvironment to one that promotes functional tissue formation, biologic scaffolds have the potential to shorten the time to complete healing, prevent advancement of these

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TAKE-HOME MESSAGES

- Tissue Engineering Regenerative Medicine (TERM) approaches for chronic nonhealing skin wounds holds therapeutic promise.
- True regeneration is limited to the epidermis; deeper wounds heal by inflammation and scar tissue formation.
- Biologic scaffolds comprising the ECM have been shown to promote constructive remodeling in nondermal tissues.
- Degradation of ECM scaffolds results in the formation of cryptic peptides with relevant biologic activities.
- Signaling molecules released from biologic scaffolds contribute to recruitment of endogenous stem cells to the site of interest.
- Signaling molecules from biologic scaffolds modulate the innate immune response from an M1 phenotype toward a more constructive M2 phenotype.
- Optimal formulations of ECM scaffolds for the treatment of nonhealing wounds have yet to be identified, but even suboptimal use has resulted in promising outcomes.

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wounds to deeper structures, and result in improved cosmetic outcomes.

AUTHOR DISCLOSURE AND GHOSTWRITING

No competing financial interests exist. The content of this article was expressly written by the authors listed. No ghostwriters were used to write this article.

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Abbreviations and Acronyms

ECM = extracellular matrix
FDA = Food and Drug Administration
FGF = fibroblast growth factor
GAG = glycosaminoglycan
HGF = hepatocyte growth factor
IGF = insulin-like growth factor
IL = interleukin
MMP = matrix metalloproteinase
PDGF = platelet-derived growth factor
SIS = small intestinal submucosa
TERM = tissue engineering and regenerative medicine
TGF = transforming growth factor
UBM = urinary bladder matrix
VEGF = vascular endothelial growth factor