D-More

True Beauty by Design

Collagen News

Throughout the years companies around the world have developed and marketed collagen-containing products to aid in wound healing. D More Industries Corporation is the only company using FDA, and the EC and Japanese Ministry of Health approved collagen, for cosmetic purposes.

Conclusive, scientific understanding of how our body uses topically placed collagen to enhance healing is well known. There is a rapidly increasing interest in all areas and purposes for topically applied collagen, indicating that collagen usage as such is very important for skin repair. D More Industries Corporation is beginning it's own clinical study, under professional guidance, and is committed, as soon as data is available, to add to the current growing number of supporting documents indicating the general health benefits associated with the application of topical collagen.

Dermatologists use several types of peels along with microdermabrasion machines to remove imperfections and aged skin from the epidermis. But even after a milder peel such as an AHA peel, it is common to experience some temporary flaking or scaling, redness and dryness of the skin. However, these conditions will disappear as the skin adjusts to treatment. After a TCA or Phenol peel, your doctor may prescribe a mild pain medication to relieve any tingling or throbbing you may feel. If tape was used to cover your face, it will be removed after a day or two. A crust or scab will form on the treated area. To help your face heal properly, it is essential that you follow your doctor's specific post-operative instructions. Both TCA and Phenol peels can cause significant swelling depending on the strength of the peel. Phenol peels have actually been known to cause such extreme swelling in the eye region that your eyes may temporarily shut for a short period of time. Someone will need to help care for you for a couple of days. You may also be limited to a liquid diet and advised not to talk very much during the first few days of recovery.

Microdermabrasion, depending on the aggressiveness of application, can cause abrasions (wounds) on the skin. Both microdermabrasion and peels relate to the wounding of the top surfaces of our skin, where abuse from normal day-to-day environmental impact contributes to premature aging; UV sun rays being the greatest offender. But these wounds are meant to heal and stimulate the growth beautiful new skin; this is where collagen comes into play.

Multiple independent university studies of wound healing have clearly indicated the essential role of collagen in the bonding of wound margins resulting in a strong closure and healing process.

There are several benefits to topical use of collagen in tissue repair. Adding D More's collagen to a treatment not only short-circuits the fibroblasts' delayed generation of collagen, but also accelerates the rate of healing. Collagen works as a protective layer to the skin from environmental pollutants and free radicals and also acts as a natural moisturizer by attracting and binding to water molecules. Collagen also works very effectively in delivering nutrients to skin cells such as antioxidants, vitamins, anti-irritants and anti-inflammatory which are essential for healthy tissue regeneration and integral part of our composition. Collagen strengthens new skin tissue over time. These are just a few of the benefits collagen provides. A sample of supporting articles to the importance of topical use of collagen for wound healing is provided below.

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Use of a Lyophilized Bovine Collagen Matrix in Postoperative Wound Healing

Steven A. Kolenik, III, MD, Thomas W. McGovern, MD, and David J. Leffell, MD

Background. Immediate reconstruction is the preferred approach to the management of defects following Mohs micrographic surgery. In a minority of patients, however, reconstruction is contraindicated, and a long-term biological dressing that stimulates wound healing and minimizes wound care is desirable.

Objective. We wanted to assess the utility of a lyophilized, type I bovine collagen matrix (*SkinTemp*) in wound care and wound healing following Mohs micrographic surgery.

Methods. Fifteen patients were treated with a bovine collagen matrix following Mohs micrographic surgery. Study wounds were evaluated for time to complete granulation, time to complete epithelialization, and adverse reactions including infection and allergy. The time to complete healing (granulation and epithelialization) for this group was compared to 15 size- and site-matched surgical defects.

Results. The use of bovine collagen matrix provided more rapid wound healing than traditional second intention healing at all anatomic sites studied. The time to complete healing averaged 6.1 weeks with bovine collagen matrix versus 9.4 weeks for the control group. Use of bovine collagen matrix required an average of 3.0 dressing changes weekly compared to 7.0 changes weekly in the control group. There were no wound infections or allergic reactions to it.

Conclusions. A Type I bovine collagen matrix provided a safe, readily available alternative to traditional methods of second intention healing. It minimized wound care while reducing the time for complete healing. A larger study should be performed to confirm the results of this pilot study.

Dermatologic Surgery - Department of Dermatology,

Yale University School of Medicine,

New Haven, Connecticut 06520-8059, USA.
Volume 25 Issue 4 Page 303 - April 1999
doi:10.1046/j.1524-4725.1999.08230.x

Steven F. Swaim, DVM, MS, Auburn University, Auburn, Alabama
ACVS Symposium Equine and Small Animal Proceedings , October 9, 2003

As with other medical disciplines, wound management has advanced considerably in recent years. This includes the development of wound healing stimulants that work at the cellular level to enhance wound healing. In addition, collagen is being used topically to enhance healing; bandage materials are being used uniquely to deliver medications to wounds; and an acrylate copolymer can be used to provide an optimal healing environment for special wounds with intact skin.

Auburn University, Auburn – Alabama

Potential role of heterologous collagen in promoting cutaneous wound repair in rats.

Mian M, Aloisi R, Benetti D, Rosini S, Fantozzi R.

The effect of native bovine tendon type-I collagen sponges (CONDRESS) on wound repair was evaluated by employing an experimental animal (rat) model which utilized subcutaneously implanted collagen and polyurethane sponges. Lesions were also created in the control groups with the exception that implants were omitted. The fusion of the hypodermal layer was selected as the index of wound repair expressed as % healing. In order to assess the extent of the healing process, parameters of clinical evaluation such as exudate volume, number of polymorphonuclears (PMNs) and macrophages (MOs) were also determined. All studies were effected at time intervals of 24, 48 and 72 h post wounding and implantation. The collagen-treated groups showed a greater healing capacity as compared to the polyurethane sponge-treated and control groups. Likewise, the exudate volume, number of leukocytes and mononuclear-type cells were all significantly higher for the collagen-treated animals than those of the polyurethane sponge-treated and control ones. Furthermore, the healthier appearance of the artificially produced wounds in the collagen sponge-treated groups (when compared to the others after 24 h) further confirmed collagen's validity in the treatment of wounds.

Department of Pharmacology, University of Milan, Italy.
PMID: 1639586 [PubMed - indexed for MEDLINE]

Lyophilized type-I collagen and chronic leg ulcers.

Mian E, Mian M, Beghe F.

Lyophilized Type I collagen (L.C.) can stimulate wound healing by recruiting a number of different cell types (i.e. platelets and macrophages) and proteins (i.e. fibronectin). Platelets and macrophages produce locally-acting growth factors that in turn induce fibroblast and epidermal migration, angiogenesis and increase matrix synthesis. Chronic leg ulcers (C.L.U.) are the end result of microvascular failure owing to ischemia and stasis. When L.C. has been used in the treatment of C.L.U. we have observed that: a) it is significantly more effective in stimulating the healing of chronic venous ulcers when compared to hydrocolloids (p less than .05), the two products being applied upon half of the same ulcer; b) in the treatment of C.L.U. due to arterial obstruction L.C. is more effective than hydrocolloids without achieving statistical significance; c) it is very effective in the treatment of C.L.U. in thalassaemic patients; d) telethermographic studies have demonstrated an increase of blood perfusion and histological studies have shown the stimulation of angiogenesis, fibropoiesis and epidermal growth; e) the application of L.C. determines the maximum obtainable increase also under conditions of proven cicatrization difficulty; and f) enzymatic degradation of L.C. has not promoted any bacterial infection and no local or generalized sensibilization phenomena have been observed. We can conclude that L.C. is a pharmacological approach to wound healing, directly interfering with cellular and non-cellular components, and significantly improves the reparative process when delayed.

Dermatological Clinic, University of Pisa, Italy.
PMID: 1725286 [PubMed - indexed for MEDLINE]
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Collagen as a pharmacological approach in wound healing.
Mian M, Beghe F, Mian E.

The authors have reviewed the most important biological mechanisms involved in wound healing, the main agents that modify the healing process and the physiological and pharmacological role of collagen. Putative mechanisms of collagen in wound repair are described with particular emphasis on haemostatic effect, interaction with platelets and fibronectin, properties of increasing fluid exudate and its cellular component (macrophages) and the "scaffold" role for fibroblastic proliferation. Experimental and clinical data clearly suggest that the potential use of collagen in wound repair and its main therapeutical applications: treatment chronic leg ulcers and pressure sores, burns, urological surgery, gynaecological surgery, dentistry and oral surgery, reconstructive surgery, abdominal and vascular surgery, orthopaedy.

Department of Pharmacology, University of Milan, Italy.
Publication Types: Review, Tutorial - PMID: 1639580 [PubMed - indexed for MEDLINE]

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The in vivo effect of hyaluronan associated protein-collagen complex on wound repair.

Cabrera RC, Siebert JW, Eidelman Y, Gold LI, Longaker MT, Garg HG.

Fetal skin wounds heal without scarring, however the underlying mechanisms remain unknown. Immunohistochemical staining and biochemical studies indicate the deposition of a collagen repair matrix that is highly organized. We have previously described a unique hyaluronan associated protein-collagen complex (HA-PC) profile present during the period of scarless healing in the sheep fetus. In this study, we examined the biologic activity of this HA-PC in an in vivo model of adult rat wound repair. A total of 84 incisional and 84 excisional wounds were examined by histology, TGF-beta immunocytochemistry and computer planimetry (excisional wounds only). Planimetry of the excisional wounds demonstrated the mean wound area remaining at day 1 was 88.7% for the control and 63.6% for the treated ($p<0.01$). At day 2, mean wound area was 81.5% for the control and 63.6% for the treated ($p<0.01$). At day 4, mean wound area was 56.6% for the control and 41.9% for the treated ($p<0.01$). At day 7, mean wound area was 26.9% for the control and 16.8% for the treated ($p<0.01$). At day 14, mean wound area was 7.9% for the control and 3.4% for the treated ($p<0.05$). Collagen organization was judged to be greater in the treated compared to control wounds, with a mean organization score of 2.3 vs. 1.9 ($p=0.0596$; Wilcoxon Signed Rank Sum Test). There were significantly more neutrophils at the wound margin of the treated compared to control wounds, 4.0 vs. 2.7 ($p=0.038$; Paired Two Tailed Student's t-Test). There was no difference in the number of microphages at the wound margin of the treated compared to control wounds, 6.15 vs. 6.0 ($p>0.05$). TGFbeta1 and beta2 staining was decreased whereas TGFbeta3 staining was increased in the HA-PC treated wounds. These results suggest that compared to control wounds HA-PC (hyaluronan associated protein-collagen) treated wounds heal more quickly, with more organized collagen, more neutrophils at the wound margin and increased TGFbeta3 expression. Furthermore, these data suggest that the manipulation of scarring in adult wounds is possible by the addition of proteins present in fetal skin.

Institute of Reconstructive Plastic Surgery,
New York University Medical Center, USA.
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Collagen-based wound dressing: effects of hyaluronic acid and fibronectin on wound healing.

Doillon CJ, Silver FH.

Our previous studies have shown that a collagen-based wound dressing induces the spatial deposition of wound tissue. This study was conducted to determine the effects of hyaluronic acid and fibronectin on wound healing. These macromolecules play an important role in wound healing, embryonic development and cellular migration in vitro. The effects of the addition of varying levels of fibronectin and hyaluronate to a collagen sponge were studied. Low levels of both hyaluronate and fibronectin modified the structure of the implant, **and resulted in increased chemoattraction, replication and collagen deposition** in an in vivo wound healing model.

PMID: 3955155 [PubMed - indexed for MEDLINE]

ORTHOTEERS SYLLABUS - *British*

WOUND HEALING

The process by which tissue repair takes place is termed wound healing and is comprised of a continuous sequence of inflammation and repair, in which epithelial, endothelial, inflammatory cells, platelets and fibroblasts briefly come together outside their normal domains, interact to restore a semblance of their usual discipline and having done so resume their normal function.

The process of wound repair differs little from one kind of tissue to another and is generally independent of the form of injury. Although the different elements of the wound healing process occur in a continuous, integrated manner, it is convenient to divide the overall process into three overlapping phases and several natural components for descriptive purposes.

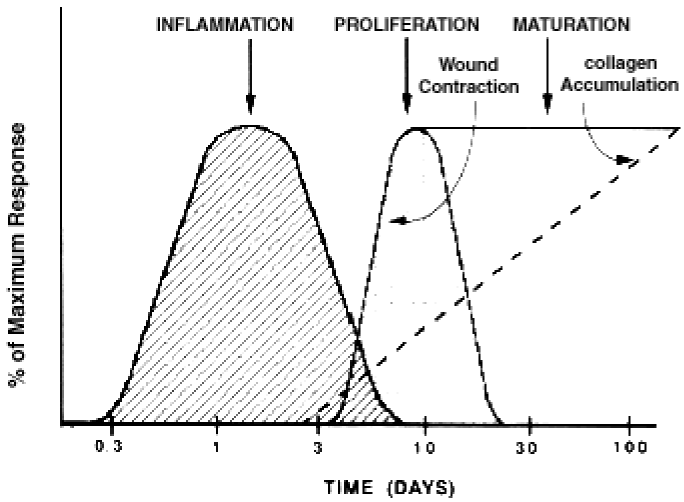

Fig. 1. Phases of wound repair. Wound healing has been arbitrarily divided into three phases: inflammation, proliferation and maturation

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Inflammatory Phase (Day 0-5)

The healing response is initiated at the moment of injury. Surgical or traumatic wounds disrupt the tissue architecture and cause haemorrhage. Initially, blood fills the wound defect and exposure of this blood to collagen in the wound leads to platelet degranulation and activation of Hageman factor [1]. This in turn sets into motion a number of biological amplification systems including the complement kinin and clotting cascades and plasmin generation. These serve to amplify the original injury signal and lead not only to clot formation, which unites the wound edges, but also to the accumulation of a number of mitogens and chemoattractants at the site of wounding [2].

Production of both kinins and prostaglandins leads to vasodilatation and increased small vessel permeability in the region of the wound [3]. This results in oedema in the area of the injury and is responsible for the pain and swelling which occurs early after injury. Within 6 h, circulating immune cells start to appear in the wound. Polymorphonuclear leucocytes (PMN) are the first blood leucocytes to enter the wound site. They initially appear in the wound shortly after injury and subsequently their numbers increase steadily, peaking at 24-48 h [4]. Their main function appears to be phagocytosis of the bacteria which have been introduced into the wound during injury. The presence of PMN in the wound following injury does not appear to be essential in order for normal wound healing to take place [5, 6], with healing proceeding normally in their absence provided that bacterial contamination has not occurred. In the absence of infection, PMN have a relatively short life span in the wound and their numbers decrease rapidly after the third day [7].

The next cellular, immune element to enter the wound are macrophages. These cells are derived from circulating monocytes by a combination of migration and chemotaxis. They first appear within 48-96 h post-injury and reach a peak around the third day post-injury [4]. These macrophages have a much longer life span than the PMN and persist in the wound until healing is complete. Their appearance is followed somewhat later by T lymphocytes, which appear in significant numbers around the fifth day post-injury, with peak numbers occurring about the seventh day after injury. In contrast to PMN, the presence and activation of both macrophages and lymphocytes in the wound is critical to the progress of the normal healing process [8, 9].

Macrophages just like neutrophils phagocytose and digest pathological organisms and tissue debris. In addition, macrophages release a plethora of biologically active substances. Many of these substances facilitate the recruitment of additional inflammatory cells and aid the macrophage in tissue decontamination and debridement; in addition growth factors and other substances are also released which are necessary for the initiation and propagation of granulation tissue formation. These intercellular transmitters are known collectively as cytokines.

Proliferative Phase (Day 3-14)

In the absence of significant infection or contamination the inflammatory phase is short, and after the wound has been successfully cleared of devitalized and unwanted material it gives way to the proliferative phase of healing. The proliferative phase is characterized by the formation of granulation tissue in the wound. Granulation tissue consists of a combination of cellular elements, including fibroblasts and inflammatory cells, along with new capillaries embedded in a loose extra cellular matrix of collagen, fibronectin and hyaluronic acid. Fibroblasts first appear in significant numbers in the wound on the third day post-injury and achieve peak numbers around the seventh day [4]. This rapid expansion in the fibroblast population at the wound site occurs via a combination of proliferation and migration [10]. Fibroblasts are derived from local mesenchymal cells, particularly those associated with blood vessel adventitia [11], which are induced to proliferate and attracted into the wound by a combination of cytokines produced initially by platelets and subsequently by macrophages and lymphocytes (Table 1). Fibroblasts are the primary synthetic element in the repair process and are responsible for production of the majority of structural proteins used during tissue reconstruction. In particular, fibroblasts produce large quantities of collagen, a family of triple-chain glycoproteins, which form the main constituent of the extracellular wound matrix and which are ultimately responsible for imparting tensile strength to the scar. Collagen is first detected in the wound around the third day post-injury [12, 13], and thereafter the levels increase rapidly for approximately 3 weeks. It then continues to accumulate at a more gradual pace for up to 3 months post wounding [10]. The collagen is initially deposited in a seemingly haphazard fashion and these individual collagen fibrils are subsequently reorganized, by cross-linking, into regularly aligned bundles oriented along the lines of stress in the healing wound. Fibroblasts are also responsible for the production of other matrix constituents including fibronectin, hyaluronic acid and the glycosaminoglycans [14]. The process of fibroblast proliferation and synthetic activity is known as fibroplasia.

	Proliferation	Chemotaxis	Collagen synthesis
TGF-β	↑↓	↑	↑
bFGF	↑		↑
MDGF	↑	↑	
IL-1		↑	↑↓
PDGF	↑	↑	
TNF-α		↑	↑↓
FIF		↓	
FAF	↑		↑
IFN-γ	↑↓		↓
IFN-α		↓	
IFN-β		↓	

Table 1. Effects of cytokines on fibroblast activities in vitro

TGF-β, transforming growth factor-β; bFGF, basic fibroblast growth factor; MDGF, macrophage-derived growth factor; IL-1, interleukin-1; FAF, fibroblast activation factor; PDGF, platelet derived growth factor; TNF-α, tumour necrosis factor-α; FIF, fibroblast inhibitory factor; IFN, interferon.

Revascularization of the wound proceeds in parallel with fibroplasia. Capillary buds sprout from blood vessels adjacent to the wound and extend into the wound space. On the second day post-injury, endothelial cells from the side of the venule closest to the wound begin to migrate in response to angiogenic stimuli. These capillary sprouts eventually branch at their tips and join to form capillary loops, through which blood begins to flow. New sprouts then extend from these loops to form a capillary plexus [15, 16]. The soluble factors responsible for angiogenesis remain incompletely defined. It appears that angiogenesis occurs by a combination of proliferation and migration. Putative mediators for endothelial cell growth and chemotaxis include cytokines produced by platelets, macrophages and lymphocytes in the wound [17, 18], low oxygen tension [19], lactic acid [20] and biogenic amines [21]. Of the potential cytokine mediators of neovascularization basic fibroblast growth factor (bFGF), acidic FGF (aFGF), transforming growth factors-α and β (TGF-α and -β) and epidermal growth factor (EGF) have all been shown to be potent stimuli for new vessel formation [22-24]. FGF, in particular, has been shown to be a potent inducer of in vivo neovascularization [25, 26].

While these events are proceeding deep in the wound, restoration of epithelial integrity is taking place at the wound surface. Re-epithelialization of the wound begins within a couple of hours of the injury. Epithelial cells, arising from either the wound margins or residual dermal epithelial appendages within the wound bed, begin to migrate under the scab and over the underlying viable connective tissue. The epidermis immediately adjacent to the wound edge begins thickening within 24 h after injury. Marginal basal cells at the edge of the wound loose their firm attachment to the underlying dermis, enlarge and begin to migrate across the surface of the provisional matrix filling the wound. Fixed basal cells in a zone near the cut edge undergo a series of rapid mitotic divisions, and these cells appear to migrate by moving over one another in a leapfrog fashion until the defect is covered [27, 28]. Once the defect is bridged, the migrating epithelial cells loose their flattened appearance, become more columnar in shape and increase in mitotic activity. Layering of the epithelium is re-established and the surface layer eventually keratinized [29]. Reepithelialization is complete in less than 48 h in the case of approximated incised wounds, but may take substantially longer in the case of larger wounds where there is a significant tissue defect. If only the epithelium is damaged, such as occurs in split thickness skin graft donor sites, then repair consists primarily of re-epithelization with minimal or absent fibroplasia and granulation tissue formation. The stimuli for re-epithelization remain incompletely determined, but it appears that the process is mediated by a combination of loss of contact inhibition, exposure of constituents of the extracellular matrix, particularly fibronectin [30], and by cytokines produced by immune mononuclear cells [31]. EGF, TGF-β, bFGF, platelet-derived growth factor (PDGF) and insulinlike growth factor-λ (IGF-λ) in particular, have been shown to promote epithelialization [32].

Maturation Phase (Day 7 to I Year)

Almost as soon as the extracellular matrix is laid down, its reorganization begins. Initially, the extracellular matrix is rich in fibronectin, which forms a provisional fibre network. This serves not only as a substratum for migration and ingrowth of cells, but also as a template for collagen deposition by fibroblasts [33]. There are also significant quantities of hyaluronic acid and large molecular weight proteoglycans present, which contribute to the gel-like consistency of the extracellular matrix and aid cellular infiltration. Collagen rapidly becomes the predominant constituent of the matrix. The initially randomly distributed collagen fibres become cross-linked and aggregated into fibrillar bundles, which gradually provide the healing tissue with increasing stiffness and tensile strength [34]. After a 5-day lag period, which corresponds to early granulation tissue formation and a matrix largely composed of fibronectin and hyaluronic acid, there is a rapid increase in wound breaking strength due to collagen fibrogenesis. The subsequent rate of gain in wound tensile strength is slow, with the wound having gained only 20% of its final strength after 3 weeks. The final strength of the wound remains less than that of uninjured skin, with the maximum breaking strength of the scar reaching only 70% of that of the intact skin [34].

This gradual gain in tensile strength is due not only to continuing collagen deposition, but also to collagen remodelling, with formation of larger collagen bundles [35] and alteration of intermolecular crosslinking [36]. Collagen remodelling during scar formation is dependent on both continued collagen synthesis and collagen catabolism. The degradation of wound collagen is controlled by a variety of collagenase enzymes, and the net increase in wound collagen is determined by the balance of these opposing mechanisms. The high rate of collagen synthesis within the wound returns to normal tissue levels by 6-12 months [37], while active remodelling of the scar continues for up to 1 year after injury and indeed appears to continue at a very slow rate for life.

As remodelling progresses, there is a gradual reduction in the cellularity and vascularity of the reparative tissue which results in the formation of a relatively avascular and acellular collagen scar. Grossly this can be observed as a reduction in erythema associated with the earlier scar and some reduction in the scar volume, resulting in a pale thin scar. This is normally a desirable feature of healing; however, in some cases shrinkage of the scar may give rise to an undesirable reduction in skin mobility resulting in contracture.

Wound contraction, i. e. inward movement of the wound edge, is a further important element in the healing process and should be distinguished from contracture. Sharply incised wounds without significant tissue loss, approximated early after injury, heal rapidly without the need for significant reduction in the wound volume. Such wounds are described as having healed by primary intention. Large wounds, however, particularly those associated with significant tissue loss, heal by secondary intention, with granulation tissue gradually filling the defect and epithelization proceeding slowly from the wound edges. Contraction of the wound edges can lead to a significant reduction in the quantity of granulation tissue required to fill the wound defect and a reduction in the area requiring reepithelization, with a consequent reduction in scar volume. Contraction is only undesirable where it leads to unacceptable tissue distortion and an unsatisfactory cosmetic result. Although contraction normally accounts for a larger part of overall wound closure in looseskinned animals, it still accounts for a significant proportion of the healing process in man, particularly in areas where the skin is not tightly bound down to underlying structures, such as on the back, neck and forearms. Initially following injury, where the wound edges are not approximated, there is a slight retraction of the wound edges due to the release of normal elastic tension in the skin, with a resultant increase in wound volume. The wound area starts to decrease rapidly from the third day onwards. While this is due in part to reepithelization, the main reason is an inward movement of the uninjured skin edges. Wound contraction usually begins around the fifth day postwounding and is complete by 12-15 days after wounding [38-40]. Fibroblasts within the wound appear to be responsible for providing the force for this contractile activity [41]. It was initially felt that specialized fibroblasts called myofibroblasts provided the motive force for wound contraction via a musclelike cell contraction [42-44]. More recent studies reveal that wound contraction occurs as a result of an interaction between fibroblast locomotion and collagen reorganization [41, 45]. The contraction is thought to be mediated via the attachment of collagen fibrils to cell surface receptors [46], with the resulting tractional forces generated by cell motility bringing the attached collagen fibrils closer together and eventually compacting them [47].

The regulation of wound contraction remains poorly defined. Information regarding the effects of specific cytokines on contraction is limited and often conflicting. TGF-β has been found to promote contraction even in the absence of serum [48, 49]; PDGF has also been found to either increase contraction [50] or have no effect [49], while both FGF and EGF have been found by different authors to either have no effect or cause a moderate enhancement of contraction [48-50].

Scar Formation

As mentioned previously, the process of wound healing is essentially similar in all tissues and is relatively independent of the mode of injury; however, slight variation in the relative contribution of the different elements to the overall result may occur. The final product of the healing process is a scar. This relatively avascular and acellular mass of collagen serves to restore tissue continuity, strength and function. Delays in the healing process cause the prolonged presence of wounds, while abnormalities of the healing process may lead to abnormal scar formation. Successful completion of wound healing may not always yield the desired clinical result, particularly where the final cosmetic appearance of the scar is of primary importance.

Collagen and the Phases of Wound Healing

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Collagen is the body's most abundant protein. It is found where strength, structure, and elasticity are needed for example, in the skin, bone, and fascia. On the molecular level, collagen has a characteristic triple-helix structure, and each protein molecule is composed of three separate polypeptide chains. Through complicated chemical activities, these structures are assembled into fibrils, then bundles of fibers, and finally tissue.

Healing Phase	**Actions of Collagen**
Inflammatory Phase • Hemostasis stops further blood loss. • Vasodilators permits migration of neutrophils to fight infection. • neutrophils attract macrophages to help remove debris.	• Assists with hemostasis[3] • Attracts macrophages with chemo-attractant properties • Causes natural cleansing due to inflammatory infiltration[4]

• Macrophages attract fibroblasts to the wound site to begin collagen synthesis	
Proliferation Phase • Fibroblasts appear within the wound and initiate collagen synthesis. • Granulation tissue(or connective/scar tissue) develops, consisting of capillary loops supported in a scaffolding of collagen fibers.	• Acts as a scaffold for fibroblast attachment [1] • Attracts additional fibroblasts to the wound site[1] • In a matrix structure, becomes a template for new tissue growth, as the primary collage structure presents attachment sites for fibroblasts[1]
Maturation Phase • Connective tissue matrix reorganizes. • Collagen fibrils consolidate into thicker, more dense fibers. • Cells gain more tensile strength.	• Imparts strength to the new tissue over time[5] • Enhances the deposition of oriented, organized collagen fibers characteristic of the remodeling phase of wound healing (suggested by some studies)[6]

A wound is described as "any disruption to the anatomic or physiologic function of tissue." At the exact moment an injury occurs, a complex series of events involving collagen is initiated, eventually progressing to tissue repair (see above). In addition to understanding the above-mentioned actions, It Is Important for clinicians to know that collagen matrices adhere well to wounds can become a template for new tissue growth, absorbs many times its weight in fluids, and effectively supports new tissue growth.[1]

References

1. Pachence JM, Berg RA, Silver FH. Collagen: Its Place in the Medical Device Industry *MD&DI*, January 1967;49-55.
2. Marcus AJ Collagen-induced platelet interactions in Tarnoff OD, Forbes CO(editors) *Disorders of Hemostasis*, Philadelphia, Saunders, 1991; 75-140.

3. Chiang TM The role of protein phosphatases 1 and 2A in collagen platelet interactions, *Arch Biochem Biophys* 1993,302 56-63.
4. Chvapil M, Chvapil BS, Gwen JA, Comparative study of four wound dressings on epithelialization of partial-thickness wounds in pigs; *J Trauma* 1997;27:276-282.
5. Brenner MA, Tracking the diabetic foot. Adjunctive treatment with collagen material, *Advances in Wound Care* 1994;7(6):44-52.
6. Doillon, CJ. Silver FH, Collagen-based wound dressing: Effects of Hyaluronic acid and fibronectin on wound healing,
Biomaterials 1986 7:3-8.
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Molecular motor implicated in tissue remodeling

St. Louis, Sept. 30, 2004--A well-known enzyme present in the skin and other tissues turns out to be a molecule-sized motor that extracts its fuel from the road it runs on(collagen), according to researchers at Washington University School of Medicine in St. Louis. Their discovery appears in the Oct. 1 issue of Science.

The enzyme, MMP-1, is a member of a group of enzymes that breaks down collagen, a fibrous substance that constitutes the foundation of the extracellular matrix that supports the cells in the body's tissues.

"By digesting collagen, enzymes such as MMP-1 initiate tissue remodeling, which can have a variety of purposes from organ development to tissue repair to metastatic invasion of tumors," says senior author Gregory Goldberg, Ph.D., professor of dermatology and of biochemistry and molecular biophysics. "Because they participate in all basic tissue metabolism, we want to understand how they function."

Goldberg and his colleagues Savees Saffarian, Ivan Collier, Barry Marmer and Elliot Elson found that MMP-1 operates as a molecular motor--a molecule that converts chemical energy into motion. "This is the only extracellular motor known," says Elson, Ph.D., coauthor and professor of biochemistry and molecular biophysics.

The research team discovered that MMP-1 moves along a collagen filament with a net unidirectional motion. One-way motion indicates that energy is being utilized, so the team looked for an energy source.

While most molecules that act as motors are inside cells and get their energy from a ubiquitous high-energy molecule called ATP, the team found that MMP-1 gets its energy by breaking the molecular bonds in the collagen filament it is attached to.

"In fact," Goldberg says, "with our model, a whole new principle emerges in which molecular motors in the extracellular matrix operate by extracting energy from the very track they move upon."

The researchers propose that the molecular motor contributes to restructuring the extracellular support matrix during tissue growth and development or wound repair or even during cancerous invasion of tissues. Because MMP-1 moves directionally, it can serve as a clutch, assisting cell locomotion along networks of collagen in tissues. Further, motion along the precisely aligned collagen filaments directs the proper development of individual tissue types.

The model of MMP-1 action revealed by Goldberg and his colleagues might help explain how the enzymes that digest collagen serve constructive purposes. "The enzymes aren't loose and disorganized where they would just end up destroying the matrix," Goldberg states. "By mechanisms that we are exploring further, they create a relation between cells and the structures in the matrix. It's a very elegant system."

Saffarian S, Collier IE, Marmer BL, Elson EL, Goldberg G. Interstitial collagenase is a Brownian ratchet driven by proteolysis of collagen. Science, Oct. 1, 2004.

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Washington University School of Medicine's full-time and volunteer faculty physicians also are the medical staff of Barnes-Jewish and St. Louis Children's hospitals. The School of Medicine is one of the leading medical research, teaching and patient care institutions in the nation, currently ranked second in the nation by U.S. News & World Report. Through its affiliations with Barnes-Jewish and St. Louis Children's hospitals, the School of Medicine is linked to BJC HealthCare.

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