Acute wound healing
An overview

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The past 2 decades have produced more advances in wound care than have the previous 2000 years as a result of rapid expansion in the knowledge of the healing process at the molecular level. The coordinated interplay of technology and expanding scientific knowledge has provided wound-care methods that have greatly improved the ability to heal wounds with few complications. These advances serve as a prelude to the impetus that is likely to come in the future.

Two broad categories exist for the classification of wounds: chronic and acute. Acute wounds undergo a complex interactive process involving a variety of cell types that leads to a healed wound. Conversely, chronic wounds have proceeded through portions of the repair process without establishing a functional anatomic result [1]. The present discussion focuses on the healing of acute wounds.

Although the wound-healing process varies among different tissue types, there are more similarities than differences between them. In this discussion, skin is considered as a representative tissue type. There are also different types of acute skin wounds, including incisional wounds, partial thickness injuries, and wounds involving significant tissue loss. Different types of wounds involve different phases of the healing process to varying degrees, although the phases themselves remain the same.

Phases of wound healing

Healing of an acute wound follows a predictable chain of events. This chain of events occurs in a carefully regulated fashion that is reproducible from wound to wound. The phases of wound healing are overlapping, but are described in a linear fashion for the purpose of clarity. The five phases that characterize wound healing include (1) hemostasis, (2) inflammation, (3) cellular migration and proliferation, (4) protein synthesis and wound contraction, and (5) remodeling (Fig. 1).

Hemostasis

All significant trauma creates a vascular injury and thereby initiates the molecular and cellular responses that establish hemostasis. The healing process cannot proceed until hemostasis is accomplished. Primary contributors to hemostasis include vasoconstriction, platelet aggregation, and fibrin deposition resulting from the coagulation cascades. The end product of the hemostatic process is clot formation. Clots are primarily composed of fibrin mesh and aggregated platelets along with embedded blood cells [2]. The importance of clot formation is profound. This process prevents further fluid and electrolyte loss from the wound site and limits contamination from the outside environment. Fibrin is also the mesh material in the provisional wound matrix onto which fibroblasts and other cells migrate as the healing process proceeds.

Vasoconstriction

Vasoconstriction is initiated by the release of vasoactive amines, which occurs when the dermis is
penetrated. Epinephrine is released into the peripheral circulation, whereas stimulation of the sympathetic nervous system results in local norepinephrine release. Injured cells secrete prostaglandins, such as thromboxane, that contribute further to vasoconstriction.

Platelet aggregation

Platelet aggregation is stimulated by exposure to tissue factors released by damaged cells. Platelets adhere to the vascular subendothelium and to each other in a process involving fibrinogen and von Willebrand factor [3]. Laminin, thrombospondin, and vitronectin may also be involved. As platelets aggregate and adhere, they release the contents of alpha granules, dense bodies, and lysosomes within their cytoplasm [4].

Alpha granules contain a variety of immunomodulatory and proteinaceous factors that are involved in both the early and late phases of healing. Specifically, these factors include albumin, fibrinogen, fibronectin [5], IgG, and coagulation factors V and VIII, as well as platelet-derived growth factor (PDGF), transforming growth factors α and β (TGF-α and TGF-β), fibroblast growth factor-2 (FGF-2), and platelet-derived epithelial growth factors (EGFs), and endothelial cell growth factors [6]. Of these factors, PDGF, TGF-β, and FGF-2 are the most important.

Dense bodies contain necessary fuel-providing compounds that contribute to the healing process. These compounds include calcium, serotonin, ADP, and ATP. Some of these compounds are also involved in initiation of the coagulation cascades.

Fibrin and the coagulation cascades

The coagulation cascades are composed of intrinsic and extrinsic components that are individually triggered. The intrinsic cascade is not required for normal healing, whereas the extrinsic cascade is essential [7]. The intrinsic coagulation cascade is initiated by activation of factor XII, which occurs when blood is exposed to foreign surfaces. The more critical extrinsic coagulation cascade is initiated by exposure to a “tissue factor” that binds factor VII or factor VIIa. Tissue factor is found on extravascular cell surfaces and, in particular, on adventitial fibroblasts. The actions of the intrinsic and extrinsic pathways result in the produc-
tion of thrombin, which catalyzes the conversion of fibrinogen to fibrin.

Thrombin itself stimulates increased vascular permeability in addition to facilitating the extravascular migration of inflammatory cells [8]. Fibrin forms the meshwork that stabilizes the platelet plug. It also becomes a key component of the provisional matrix that develops in the wound soon after injury. Fibrin becomes coated with vitronectin derived from serum and aggregating platelets. This action facilitates the binding of fibronectins, which are produced by fibroblasts and epithelial cells [5]. Fibronectins are the second key component of the early provisional wound matrix. The fibronectin molecule has nearly a dozen binding sites for cellular attachment [9]. These attachment sites are essential for cellular migration along the matrix. The fibrin–fibronectin matrix also traps circulating cytokines for use in the ensuing stages of healing [10].

Inadequate fibrin formation is associated with impaired wound healing. This is observed in factor XIII (fibrin-stabilizing factor) deficiency, which is thought to impair cellular adhesion and chemotaxis [11]. Any process that removes fibrin from the wound will disrupt the formation of extravascular matrix and also, consequently, will delay wound healing [12,13].

Inflammation

Inflammation is characterized by the erythema, edema, heat, and pain as first described by Hunter in 1794. At the tissue level, increased vascular permeability and the sequential migration of leukocytes into the extravascular space characterize inflammation [1]. One of the primary functions of inflammation is to bring inflammatory cells to the injured area [14]. These cells then destroy bacteria and eliminate debris from dying cells and damaged matrix so that the repair processes can proceed [15].

Although inflammation is often thought of as the second phase of wound healing, signs of inflammation, including erythema and heat, develop soon after injury as a result of vasodilation. Vasodilation follows the initial vasoconstriction that reverses 10 to 15 minutes after injury. Simultaneously, the endothelial cells lining the capillaries in the vicinity of the wound develop gaps between them, which permit the leakage of plasma from the intravascular space to the extravascular compartment [16]. The migration of fluid into the injured area generates edema, which contributes to the sensation of pain that characterizes inflammation.

The transition from vasoconstriction to vasodilation is mediated by a variety of factors. Endothelial products and mast cell-derived factors such as leukotrienes, prostaglandins, and, in particular, histamine contribute to vasodilation [17,18]. Kinins, released by protein-binding molecules in the plasma via activation of kallikrein, also contribute to this process.

Capillary leak is primarily mediated by the release of histamine, kinins, and prostaglandins. There is an additional influence from thrombin and the complement system. Complement factors C3a and C5a are significant contributors to capillary leak and also act as chemoattractants for neutrophils and monocytes [19]. Their chemotactic function is dependent on the release of TGF-β and formyl-methionyl peptides [20].

Leukocyte migration into the wounded area is stimulated by collagen, elastin breakdown products, complement factors, and immunomodulatory factors including TGF-β, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), PDGF, leukotriene B4, and platelet factor IV. Leukocytes adhere to endothelial cells lining the capillaries in the wounded area through an interaction of intracellular adhesion molecules on the endothelial cell membranes and integrins expressed on the cell surface of the leukocytes. This process is known as margination. Platelet factor IV and platelet-activating factor then increase the expression of CD11/CD18, an integrin on the neutrophil surface that facilitates transmigration of leukocytes through the endothelium [21] in a process known as diapedesis.

Migrating monocytes transform into macrophages as they migrate into the extravascular space in a process that is stimulated by chemotactic factors such as fibronectin, elastin derived from damaged matrix, complement components, enzymatically active thrombin, TGF-β, and serum factors [11]. All leukocytes require activation before they can perform their vital functions in the wound environment [22]. IL-2 and INF-α derived from T lymphocytes are involved in macrophage activation [23].

After activation, macrophages and neutrophils initiate cellular wound debridement by phagocytosing bacteria and foreign material [24]. Both cell types have surface receptors that allow them to recognize, bind, and engulf foreign material [25]. Macrophage binding receptors include the immunoglobulin-type adhesion molecule CD14 that binds lipopolysaccharide [26] and the CD11b-CD18 αβ integrin. After binding, bacteria and debris are engulfed and digested by oxygen radicals and hydrolytic enzymes within the inflammatory cells. In addition to phagocytosing debris, macrophages also contribute to its breakdown extracellularly by releasing matrix metalloproteinases (MMPs) such as collagenase and elastase into the wounded area [27].
In addition to contributing to phagocytosis, macrophages are also a primary source of cytokines that mediate later aspects of the healing process. Some macrophages primarily phagocytose foreign materials and produce MMPs, whereas others primarily produce cytokines. Unlike polymorphonuclear leukocytes, the removal of macrophages from the healing milieu will significantly alter and impede the healing process [14]. The presence or absence of polymorphonuclear leukocytes will only alter the rate of wound infection [28]. The added function of cytokine production differentiates the activities of the two cell types and makes macrophages more essential.

The role of the macrophage is complex in that this multipurpose cell is involved in many aspects of healing through the cytokines and immunomodulatory factors it produces (Fig. 2). Macrophage-produced cytokines are involved in angiogenesis, fibroblast migration and proliferation, collagen production [29], and possibly wound contraction. TGF-β, IL-1, insulin-like growth factor-1 (IGF-1), FGF-2, and PDGF are several of the more critical macrophage-derived cytokines. TGF-β regulates its own production by macrophages in an autocrine manner [30]. It also stimulates macrophages to secrete PDGF, FGF-2, TNF-α, and IL-1 [20] through binding of the epidermal growth factor receptor. Furthermore, macrophages also release nitric oxide, which may serve an antimicrobial function as well as other functions during the healing process [28]. The inhibition of nitric oxide release has been found to impair wound healing in an in vivo mouse model [31]. The complete role of nitric oxide in wound healing has yet to be fully delineated.

T lymphocytes play a crucial role in the wound-healing process as well, and the removal of circulating T lymphocytes inhibits the healing cascade [32]. Seventy to eighty percent of normal peripheral blood lymphocytes are mature T lymphocytes. B lymphocytes contribute the remaining 10% to 15% and have not been found to play any role in wound healing [33]. Typically, both CD4-positive and CD8-positive T lymphocytes are present in maximal concentrations 5 to 7 days after injury under the influence of IL-2 and various other immunomodulatory factors [34,35]. T lymphocytes—especially CD4-positive T lymphocytes—are important sources of cytokines including IL-1, IL-2, TNF-α, fibroblast activating factor, EGF, and TGF-β [36–38]. Among other functions, these factors regulate the process of T-cell proliferation and differentiation in an autocrine fashion. T cells are also the primary effectors of cell-mediated immunity and

Fig. 2. Cell interactions. Acute wound healing is dependent on a complex interplay of various inflammatory markers and cell types. Macrophages are crucial to the various phases of acute wound healing and serve as a central stimulator for several different cell types involved in wound healing.
subsets of T cells mature into cytotoxic cells capable of lysing virus-infected and foreign cells [22].

Other inflammatory cell types include eosinophils and basophils. These leukocytes are nonspecific amplifiers and effectors of specific immune responses [39]. Both eosinophils and basophils in unchecked accumulation can lead to host tissue damage, as seen in eosinophil-mediated systemic necrotizing vasculitis [33]. These cell types reach their highest concentrations in wounds 24 to 48 hours after injury, and are capable of producing TGF-α [32]. Their complete role in inflammation remains to be delineated.

As the healing process proceeds, inflammatory cells trapped within clots are sloughed [40]. Neutrophils remaining within the wound become senescent and undergo apoptosis [41]. Apoptosis is characterized by the activation of endogenous calcium-dependent endonucleases. The activation of these endonucleases results in cleavage of chromatin into oligonucleosome DNA fragments [42], and is indicative of irreversible cell death. The stimuli that lead to inflammatory cell apoptosis during tissue repair and scar formation have yet to be determined. Neutrophils are the first of the inflammatory cells to become apoptotic. They are then phagocytosed by macrophages [24]. Macrophages and lymphocytes remain in the wound for approximately 7 days and then gradually diminish in number unless a noxious stimulant of further inflammation persists. Inflammatory cell apoptosis influences antigen presentation and, probably more importantly, contributes to modulation of cytokine concentrations [16].

Cytokines

The wound-healing process is, in large part, regulated by the ordered production of cytokines that control gene activation responsible for cellular migration and proliferation and synthetic activities. As mentioned, platelets and macrophages are key cytokine sources, although many other cells produce them. Control of the release of cytokines is, in part, regulated by other cytokines and, in part, regulated by characteristics of the tissue milieu [43,44]. An often underreported signal for cytokine release is tissue hypoxia. Hypoxia has been shown to stimulate the release of TNF-α, TGF-β, vascular endothelial growth factor (VEGF), and IL-8 (IL-8) from fibroblasts, endothelial cells, and macrophages [2,36,37,45].

“Cytokine networks” exist where multiple cell types involved in the healing process have receptors for the same cytokine. This permits stimulation of multiple different activities by single cytokines [46]. This redundancy is most likely important in that different factors may play greater or lesser roles at different time points or at different sites.

Many cytokines can also stimulate several different cellular functions in a single cell, which are often dependent on the concentration of the cytokine. This further allows individual cytokines to have varying effects at different points during the healing process. TGF-β, for example, is a macrophage chemoattractant when circulating in the fentomolar range, but cannot stimulate collagen synthesis by fibroblasts until found in the nanomolar range [16]. In addition, PDGF facilitates chemotaxis for fibroblasts, but only at a 100-fold greater concentration gradient than is necessary to stimulate fibroblast proliferation [47,48].

Cellular activity is also regulated by the balance of cytokines and cytokine isoforms with conflicting activities. Cytokines such as PDGF, TGF-β, and FGF-2 accelerate collagen synthesis scar formation [49]. Other cytokines slow collagen synthesis, including the β3 isoform of TGF-β and INF-α and INF-α2b [41]. Cellular activity is, therefore, modulated by the balance of cytokines with competing functions. Loss of network balance has been implicated in chronic wound healing pathways [2].

Cellular migration and proliferation

The cellular milieu in wounds changes dramatically in the first week post acute injury. The initial fibrin–fibronectin matrix is heavily populated by inflammatory cells, whereas fibroblasts and endothelial cells will predominate as healing progresses. Re-establishment of the epithelial surface is also initiated within the first several days after injury, as is revascularization of the damaged area. Cytokine networks continue to be a part of the process as cytokine release contributes to fibroplasia, epithelialization, and angiogenesis [44]. Although much is known about the signals that stimulate the predominant activities during this phase of healing, less is known about the signals that bring these activities to a controlled end. Negative feedback mechanisms that deactivate cells after they have completed their work are also essential for normal healing.

Additional fibroblasts are required in the healing wound, in that native cells are lost or damaged in any injury. Repopulation of the wounded area with fibroblasts occurs as a result of fibroblast migration from adjacent tissues and proliferation of cells in the wound. In addition, undifferentiated cells in the vicinity of the wound may transform into fibroblasts under the influence of cytokines in the wound milieu [50].
Factors that stimulate fibroblast migration include PDGF [48], TGF-β [50], EGF [51], and fibronectin [18]. Upregulation of cell membrane integrin receptors that bind fibronectin and fibrin in the provisional wound matrix is required for fibroblasts to migrate [52,53], and PDGF [54,55] and TGF-β [50] both contribute to the migratory process in this manner.

Integrin expression is, therefore, vital to the migration of fibroblasts and other cell types. There are over 20 different integrin molecules, and most have α and β subunits [21]. Different cells express different integrins, and individual cells can often express more than one integrin, often under the influence of varied cytokines. Cellular migration requires cell membrane-bound integrins to be bound to fibronectin in the extracellular matrix [56]. A migrating cell then develops lamellipodia that extend outward until another binding site is detected in the matrix [57]. By releasing the primary binding site and pulling itself toward the second site, the cell migrates, using the new site as an anchor [17]. Fibronectin fragments stimulate this migratory process [18]. The orientation of fibers in the matrix also influences cellular migration, in that cells tend to migrate along fibers and not across them. The ability of fibroblasts to migrate may be impeded by residual debris in the wound environment. To facilitate migration through such debris, fibroblasts secrete several proteolytic enzymes including MMP-1, gelatinase (MMP-2), and stromelysin (MMP-3) [58,59]. TGF-β stimulates fibroblasts to secrete these enzymes [30,60,61].

The proliferation of residual fibroblasts in the wounded area, as well as fibroblasts that have migrated to it, is regulated by a variety of cytokines. PDGF and TGF-β are two of the most important cytokines involved in this process. PDGF often works in concert with IGF to facilitate fibroblast proliferation [48]. PDGF primarily stimulates cells to progress through the early G0 and G1 phases of the cell cycle [47]. IGF, which is derived primarily from hepatocytes and fibroblasts [37], then facilitates progression through the subsequent S1, G2, and M phases of the cell cycle.

Angiogenesis

The angiogenic process becomes active from day 2 after wounding [39]. Factors in the wound milieu that contribute to angiogenesis include high lactate levels, acidic pH, and, in particular, decreased oxygen tension [35]. The severe degree of hypoxia in granulation tissue most likely results from both disruption of the native vasculature and increased oxygen consumption by cells in the wound environment [40]. Proliferating cells are known to consume oxygen three to five times faster than do cells in resting phases of the cell cycle.

During angiogenesis, endothelial sprouts derive from intact capillaries at the wound periphery [62]. The sprouts grow through cellular migration and proliferation. The endothelial cells develop a curvature and begin to produce a lumen as the chain of endothelial cells elongates. Eventually, the endothelial sprout comes into contact with a sprout derived from a different capillary, and they interconnect generating a new capillary.

Endothelial migration during angiogenesis involves binding integrin domains within the provisional fibrin–fibronectin matrix in a similar manner to fibroblasts. Upregulation of αβ3 integrins is specifically associated with angiogenesis. Endothelial cell migration is also facilitated by the cell’s ability to produce MMPs that break down collagen and plasminogen activator, which facilitates movement through the matrix.

As mentioned, the angiogenic process is regulated by a variety of cytokines. The two most important cytokines that contribute to angiogenesis are FGF-2 [63]—which has also been known as basic fibroblast growth factor—and VEGF [64]. Heparin is a necessary cofactor for FGF-2 [65]. Cytokine concentrations diminish as the wounded area becomes revascularized, and this flux in angiogenic cytokines may facilitate maturation of the vascular system.

Epithelialization

Following acute injury, reconstruction of injured epithelium is crucial for re-establishment of the barrier functions of the skin. Reconstruction of injured epithelium begins almost immediately after wounding. Incisional skin injuries, with a minimal epithelial gap, are typically re-epithelialized within 24 to 48 hours after initial injury [2,66], although larger wounds can take much longer to regenerate a neoepithelium. During the first 24 hours after injury, basal cells present at the wound edge elongate and begin to migrate across the denuded wound surface. If the initial injury does not destroy epithelial appendages such as hair follicles and sweat glands, these structures also contribute migratory epithelial cells to the healing process. These cells migrate across the wounded area essentially as a monolayer. Approximately 24 hours after the initiation of cellular migration, basal cells at the wound edge and in the appendages, if present, begin to proliferate, contributing additional cells to the healing monolayer. The migration of epithelial cells continues until overlap is achieved with other epithelial cells migrating from different directions. At that point, “contact inhibition” results in cessation of cellular migration. The processes of cellular migration and proliferation
occur under the control of various cytokines including EGF [66,67], TGF-α, platelet-derived EGF, and keratinocyte growth factor (KGF, also known as FGF-7) [68]. Some derive from inflammatory cells and others derive from the epithelial cells themselves. Cellular migration may also require the secretion of MMPs to penetrate eschar or scab [69].

Epithelial cell migration requires the development of actin filaments within the cytoplasm of migratory cells and the disappearance of desmosomes and hemidesmosomes that link them to one another and to the basement membrane, respectively. At least some of these processes are dependent on changes in integrins expressed on the cell membranes [70]. It is thought that decreased calcium or increased magnesium concentrations stimulate the downregulation of the critical integrins, although the precise signal is not yet known [56].

If the epidermal basement membrane is intact, cells simply migrate over it. In wounds in which it has been destroyed, the cells initially begin to migrate over the fibrin–fibronectin provisional matrix [12,13]. As they migrate across the matrix, however, epithelial cells regenerate a new basement membrane. Re-establishment of a basement membrane under the migrating cells involves the secretion of tenasin, vitronectin, and type I and V collagens [71].

When contact inhibition is achieved, hemidesmosomes re-form between the cells and basement membrane, and tenasin and vitronectin secretion diminishes. The cells become more basaloid [72], and further cellular proliferation generates a multilaminated neoepidermis covered by keratin. The neoepidermis is similar to the native epidermis, although it is slightly thinner, the basement membrane is flatter, and rete pegs that normally penetrate the dermis are absent.

**Protein synthesis and wound contraction**

Synthesis and deposition of proteins and wound contraction are the wound-healing events that begin to predominate 4 to 5 days after wounding. The quality and quantity of matrix deposited during this phase of healing significantly influence the strength of a scar [73]. Collagen constitutes more than 50% of the protein in scar tissue, and its production is essential to the healing process [74]. Fibroblasts are responsible for the synthesis of collagen and other proteins regenerated during the repair process. Collagen synthesis is stimulated by TGF-β3, PDGF, and EGF [75]. Collagen synthesis is also affected by characteristics of the patient and the wound including age, tension, pressure, and stress [76]. Collagen synthesis continues at a maximal rate for 2 to 4 weeks and subsequently begins to slow.

Healing aberrations are often the result of aberrations in collagen deposition, although the underlying causes may vary. In diabetes, impaired activation of inflammatory cells coupled with deficiencies in other aspects of the healing process result in limited collagen deposition and impaired healing [77]. Conversely, keloid formation results from excessive collagen synthesis for which a preventative measure has yet to be found [78].

As mentioned, the initial wound matrix is composed primarily of fibrin and fibronectin. As protein synthesis accelerates, the nature of the wound matrix changes. Collagen and other proteins such as proteoglycans gradually replace fibrin as primary matrix constituents. Proteoglycans are a key component of mature matrix and are actively synthesized during this phase of healing. Additional proteins such as thrombospondin I and SPARC (secreted protein acidic rich in cysteine)—which support cellular recruitment and stimulate wound remodeling—are also produced and are found in the mature wound matrix as well [79].

Collagen makes up 25% of protein in the body and more than 50% of protein in scar tissue [74]. The concentration of collagen subtypes varies among tissues. Type I collagen predominates and makes up 80% to 90% of the collagen seen in intact dermis. The remaining 10% to 20% is type III collagen. In contrast, granulation tissue that forms soon after injury contains 30% type III collagen. Accelerated type III collagen synthesis is correlated with fibronectin secretion after injury [75]. Type II collagen is seen almost exclusively in cartilage, whereas type IV collagen is found in basement membranes. Type V collagen is found in blood vessels, whereas type VII collagen forms the anchoring fibrils of epidermal basement membrane [80].

Type I collagen consists of a triple helix involving three polypeptide chains that are synthesized separately within the fibroblast. The polypeptide chains consist of a repeating glycine-X-Y pattern, in which the X position is often proline and the Y position is often hydroxyproline. The interaction of chains initiates the formation of the triple helix, which is secreted as “procollagen” into the extracellular environment [81].

Collagen undergoes eight posttranslational steps intracellularly prior to its extracellular secretion in the form of procollagen [29]. A critical step involves hydroxylation of proline and lysine moieties within the polypeptide chains. Hydroxylation of proline and lysine requires specific enzymes and the cofactors
oxygen, vitamin C, ferrous iron, and α-ketoglutarate. Hydroxyproline is an important marker of the quantity of collagen within tissues in that it is almost exclusively found in collagen. Hydroxylysine is an essential element for cross-link formation both within and between collagen molecules [81]. Deficiencies in vitamin C (scurvy) or suppression of enzymatic activity by corticosteroids can lead to underhydroxylated collagen that is incapable of generating strong cross-links.

Procollagen-C proteinases and procollagen-N proteinases cleave the propeptide ends of the procollagen molecules after they have been secreted into the extracellular space. This decreases the solubility of the molecules and initiates the formation of fibrils. During fibril formation, collagen molecules are initially linked together by electrostatic bonds. Subsequent to this, free amino groups on lysine and hydroxylysine residues within the collagen molecules are transformed to aldehyde residues by the enzyme lysyl oxidase. The aldehyde residues interact with nontransformed lysine or hydroxlysine residues on adjacent molecules, resulting in the formation of stable covalent cross-links between the molecules [35]. These cross-links stabilize the conjoined collagen molecules as fibrils and fibers.

As mentioned, proteoglycans are also normal dermal matrix proteins that are synthesized by fibroblasts after injury. Their concentration in injured tissue gradually increases with time in a manner paralleling collagen. Proteoglycans consist of a protein core covalently linked to one or more glycosaminoglycans [82]. Proteoglycans bind proteins and alter their orientation in a manner that influences their activity. Dermatan sulfate is a proteoglycan that orients collagen molecules in a manner that facilitates fibril formation. Hyaluronan, another proteoglycan, contributes to skin’s viscoelastic properties and acts as a potent modulator of cellular migration [82].

Elastin is another component of wound matrix that provides elasticity to normal skin. It is not synthesized in response to injury and is subsequently not found in scar. This lack of elastin in scar tissue contributes to the increased stiffness and decreased elasticity of scar as compared with normal dermis.

Wound contraction begins 4 to 5 days after initial injury and actively continues for approximately 2 weeks. The process continues for a longer period of time in wounds that remain open at the end of the 2-week interval. In an open wound, the results of wound contraction are evident because wound edges draw closer to each other. In an incisional wound, wound contraction simply results in scar shortening and is less apparent. The rate of contraction varies between anatomic locations, but averages approximately 0.6 to 0.7 mm per day. The rate of contraction can often be predicted by the degree of skin laxity at the wound site. A wound on the scalp or pretibial area will contract significantly more slowly than a buttock wound. Wound shape also affects the rate of contraction, with square wounds contracting more quickly than circular wounds. Circular stomas are therefore less likely to have compromised patency secondary to contraction.

Wound contraction is characterized by a predominance of myofibroblasts at the wound periphery. Myofibroblasts are modified fibroblasts that were initially described by Gabbiani et al in 1971 [83]. The defining characteristics of myofibroblasts include actin-rich microfilaments in the cytoplasm, a multi-lobulated nucleus, and abundant rough endoplasmic reticulum that can only be discerned by electron microscopy. The time frame in which myofibroblasts are present within the wound does not correspond perfectly to the course of wound contraction, although it is fairly close. Myofibroblasts appear 4 to 6 days after initial injury and are commonly seen in the wound during the ensuing 2 to 3 weeks. Their disappearance is suspected to be via apoptosis. Although Gabbiani et al [83] postulated that these cells were the “motor” that contracted a wound, more recent work with collagen lattices has suggested that fibroblasts in the central portion of the wound may be more critical to the contraction process [42]. It is clear, however, that the process of wound contraction is cell mediated and does not require collagen synthesis. TGF-β and possibly other cytokines are involved in the wound contraction process [84].

Wound contraction is sometimes not a desirable healing event. Wound contraction across joints can produce contractures that significantly limit function. In cases in which contraction inhibition is preferred, skin grafting, especially with thicker grafts, is used to limit contraction. Splints can also limit undesirable contraction in certain anatomic locations if utilized for prolonged periods.

Remodeling

Scar remodeling begins to predominate as the primary wound-healing activity approximately 21 days after injury. The rate of collagen synthesis diminishes and reaches coincidence with the rate of collagen breakdown. The downregulation of collagen synthesis is mediated by γ-interferon [85], TNF-α [86], and collagen matrix itself [29].

Matrix metalloproteinases (MMPs) are intimately involved with the breakdown of collagen molecules
that occurs actively during the remodeling process. The MMPs have been alluded to previously and are involved in many aspects of the healing process. MMPs represent a family of at least 25 enzymes that break down different extracellular matrices [58–60]. They are produced by a variety of cell types, and different cells generally synthesize different enzymes. The MMP activity within tissues is modulated by tissue inhibitors of metalloproteinases (TIMPs) [87]. Four isoforms of TIMPs have been described [87]. The balance of MMPs and TIMPs within tissues is critical to enzyme activity and is regulated by cytokines including TGF-β, PDGF, and IL-1 [43,61,88].

All of the functions provided by MMPs during wound healing have not been clearly delineated. Elevated concentrations of MMPs are seen in chronic ulcers [77], yet deletion of MMP-3 in mice causes failure of wound contraction with a significant delay in healing [73], thereby implicating a complex regulatory pathway.

The nature of the wound matrix changes with scar remodeling. Immature scar contains a disorganized array of fine collagen fibers, which is gradually replaced by thicker fibers arranged in an orientation paralleling skin stresses. In addition, the number of cross-links both within and between molecules gradually increases. As the nature of the collagen matrix changes, it becomes less cellular through apoptosis of cells involved in the healing process. As mentioned, the ratio of type I to type III collagen changes, and the quantity of water and proteoglycans diminish. Normal skin shows a basketlike weave pattern that is never completely reproduced with scar remodeling.

Although seemingly not as complex as other aspects of the healing process, remodeling is essential to the formation of a strong wound. The remodeling process is associated with a substantial increase in wound-breaking strength. Wound strength 1 week after injury is 3% of normal dermis. After 3 weeks, when the remodeling phase begins to predominate, the wound will have only approximately 20% the strength of normal dermis. At 3 months, however, the wound will have 80% the strength of normal dermis, with the significant increase in strength resulting from the contribution of remodeling. Remodeling will continue for up to 12 months after a wound is created, although scars never regain the strength of normal dermis.

Summary

The ability to heal an injury is a biologic necessity for all organisms, with mammals lagging in proficiency when compared with lower life forms that have the ability to regenerate differentiated structures. Technology and increased scientific knowledge have established a coordinated interplay that has improved the ability to manage wounds in a logical manner, and, on occasion, to accelerate the healing process. Insight into the complex chain of events leading to the formation of scar is a necessity for every individual who attempts wound management.

References


