Cytokine manipulation of the wound

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The normal response to tissue injury is a timely and orderly reparative process that results in sustained restoration of anatomical and functional integrity [1]. Wound repair, however, is not a simple linear process but rather a complex integration of dynamic interactive processes involving cell–cell and cell–matrix interactions mediated by humoral messengers [2,3]. Unencumbered, these processes follow a specific time sequence or chronology [2]. Although the timing of the various processes is usually orderly, it is not mutually exclusive and there is a varying overlap in time [4].

Because wound healing is dynamic and the processes ideally occur in an orderly and timely manner, it is clear that time is an important variable in wound repair [4]. Clinically, categorization of wounds as acute or chronic has been based on timeliness of healing [5]. The importance in factoring time into wound healing becomes clear when one realizes that the culminative goal of much wound-healing research is to discover products and processes that can accelerate wound healing in humans [6].

The scheme of processes and mediators can be applied to all wounds. When a wound proceeds through an orderly and timely reparative process and results in a sustained restoration of anatomical and functional integrity, it is labeled an acute wound [1]. Conversely, a chronic wound is one that has failed to proceed through an orderly and timely process to produce anatomical and functional integrity, or has proceeded through the repair process without establishing a sustained anatomic and functional result [1]. Simply stated, wounds may be classified as those that repair themselves or can be repaired in an orderly and timely process (acute wounds) and those that do not (chronic wounds).

The various cellular processes in the wound-healing scheme are mediated by cytokines, growth factors, and matrix metalloproteinases (MMPs) [4]. Because the individual cellular processes appear to be capable of functioning in both acute and chronic wounds, the implication is that an impairment or imbalance in cytokines, growth factors, or MMPs in wounds promotes the establishment and maintenance of chronic wounds [7]. When comparing fluids from acute wounds to those from chronic wounds, it has been demonstrated that chronic wounds have elevated proinflammatory cytokines, high protease activity, decreased levels of the natural inhibitors to metalloproteinases, and diminished growth factor activity [5,8,9].

The role of cytokines and growth factors in wound healing

It is clear that certain proteins (polypeptides) directly regulate many of the processes that are crucial for normal wound healing, including chemotactic migration of inflammatory cells; mitosis of fibroblasts, keratinocytes, and vascular endothelial cells; neovascularization; and synthesis and degradation of extracellular matrix components [5]. These regulatory peptides, known as cytokines, include polypeptides such as the interleukins (ILs), hematopoietic colony-stimulating factors, and tissue necrosis factors [10]. They also include the various growth factors. Growth factors are synthesized and secreted by many types of cells involved in tissue repair,
including platelets, inflammatory cells, fibroblasts, epithelial cells, and vascular endothelial cells [11]. They may act on the producer cell (autocrine stimulation), adjacent cells (paracrine stimulation), or distant cells (endocrine stimulation). Substances such as cytokines that are chemotactic to inflammatory cells such as neutrophils and macrophages, or are mitogenic to cells such as fibroblasts, endothelial cells, and keratinocytes should benefit wound healing [3]. Certainly the literature is replete with examples of effects of exogenous application of cytokines for animal models of both acute and chronic wounds [12–14]. In all of those animal models, it has been suggested that wound healing would be enhanced by topical application of cytokines.

**Rationale for the use of cytokines to manipulate wound healing trajectories**

In impaired wound healing, from whatever cause, the time to healing is delayed and the wound-healing trajectory is slowed. This may be due to the wrong amount, the wrong sequence, or the wrong time course of the necessary cytokine activity. Certainly, exogenous application of cytokines would seem to be indicated if there was a deficiency of cytokines in a wound. Evidence is mounting that such is the case in chronic wounds. This deficiency could be absolute or relative, due to decreased production or secretion, more rapid breakdown, or trapping or binding of the cytokines that prevents their effective use in the healing processes [4]. Using an ELISA technique on retrieved chronic wound fluid it was demonstrated that platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and transforming growth factor β (TGF-β) levels were markedly decreased compared with acute wounds [15]. Even when cytokine growth factors are not lacking, they may not be effectively available to the wound for healing [13]. In venous stasis ulcers, macromolecular leakage—specifically fibrinogen, α macroglobulin, and albumin—leads to binding of these substances to growth factors, making them unavailable to the repair process [16]. This type of trapping has also been reported in diabetic ulcers [13].

In addition to the decreased availability of growth factors and the trapping of those that are present in chronic wounds, there is a problem with the bacterial burden [17,18]. The ever-present tissue level of bacteria in chronic wounds produces higher levels of proteases and other MMPs that further degrade the cytokines [19]. It is clear that degradation of cytokines and their receptors limits the progression of the wound-healing cascade by eliminating the mediators of the various cellular processes.

Many of the problems listed for chronic wounds are not as significant a problem for acute wounds. Bacterial loads and protease levels are much lower. Optimizing the cellular or molecular wound environment by topical application of cytokines is just beginning to be explored, in an effort to shift the gain in wound strength toward shorter times for incisional healing of both dermis and fascia [13,20,21].

Although most surgeons observe that acute wounds heal “normally” most of the time, most surgical patients view the acute healing process as a long one that is simultaneously physically limiting and often psychologically upsetting. This time is spent limited by pain, mechanical weakness, functional loss, and cosmetic changes [4]. It is therefore important to develop strategies to reduce the time of acute wound healing in order to minimize the acute wound burden and shorten the period of disability when normal healing occurs. Molecularly this can be done theoretically by identifying and modifying the timing or sequence of delivery of potent cytokine or tissue growth factor signaling peptides that are believed to be most important for regulating each phase of acute wound healing.

**Topical application of cytokines to manipulate healing of chronic wounds**

Recombinant technology has allowed for production of many cytokines in pharmacological amounts. This has resulted in attempts to optimize the cellular or molecular environment of wounds. Most data exist for chronic wounds because of their known impairments in healing. Two recent reviews of the clinical experience of topical application of cytokines to chronic wounds have been published [4,13]. These experiences suggest that several cytokines may be used to manipulate healing of chronic wounds such as pressure ulcers, diabetic neurotrophic foot ulcers, or venous stasis ulcers. The cytokines have been applied as single agents, in combination, or sequentially.

**PDGF**

PDGF serves as the paradigm for the use of a topical growth factor to enhance chronic wound healing [4]. It is the first recombinant cytokine growth factor to be approved by the United States Food and Drug Administration (USFDA) for topical application to wounds for the purpose of accelerating wound
closure. Based on preclinical results, clinical trials were first conducted with topical application of PDGF-BB for the treatment of pressure ulcers [22–24]. The initial trials were performed with PDGF-BB in a liquid carrier. To allow for a more prolonged effect of the topically applied growth factor, subsequent trials have been reported using PDGF-BB in a sodium carboxymethyl cellulose gel. Rees et al [25] demonstrated efficacy with this formulation of PDGF-BB in 124 patients with chronic pressure ulcers.

The largest clinical growth factor experience to date has been the use of PDGF-BB to treat full-thickness diabetic foot ulcers with adequate circulation [4]. The first study included 118 patients with neurotropic ulcers of greater than 8 weeks in duration [26]. The patients were debrided of all necrotic tissue and had a TcPO2 of greater than 30 mm Hg. Patients received topical application of PDGF-BB or placebo once daily until the ulcer healed or for a maximum of 20 weeks. The incidence of complete healing in patients treated with PDGF-BB was 48% (29 out of 61) versus 25% (14 out of 57) for those treated with placebo (P = 0.01). The time to complete healing was 113 days for the treatment group compared with 126 for the placebo group (P = 0.02) [26]. Four clinical trials and six clinical trials have been performed to prove the efficacy and safety, respectively, of topical PDGF-BB for the treatment of lower extremity diabetic neuropathic ulcers. The conclusion from these studies and the USFDA review is that topical PDGF-BB in a 100 μg/g becaplermin gel is safe and efficacious to enhance wound healing of diabetic foot ulcer [4,27]. In addition to pressure ulcers and diabetic ulcers, studies are under way to assess the efficacy and safety of becaplermin gel in other types of chronic wounds, such as venous stasis ulcers [13].

bFGF

The FGF family consists of at least nine homologous peptides, three of which have been used extensively in preclinical wound-healing studies (bFGF [FGF-2], aFGF [FGF-1], and keratinocyte growth factor 2 [KGF-2; also known as FGF-10]) [4,13]. Basic FGF—which is mitogenic and chemo- tactic for fibroblasts and endothelial cells, and is a stimulus for angiogenesis—has the greatest reported clinical trial experience [4]. Based on preclinical experience with contaminated animal models, the first randomized, blinded, placebo-controlled trials were conducted on patients with pressure ulcers. Fifty patients were treated with eight different dosage regimens of three different bFGF concentrations (1.0, 5.0, and 10 μg/cm²) [28]. There was a trend toward faster healing in six out of eight groups treated with topical bFGF compared with the vehicle-treated groups. When all patients receiving bFGF at two institutional sites were combined as a group, the difference between the slopes of the treated and placebo curves was significant (P < 0.05). When the data were analyzed in terms of the number of patients achieving a 70% volume reduction, 21 out of 35 patients receiving bFGF responded, versus 4 out of 14 patients in the placebo group. This outcome was significantly different (P = 0.047) [28].

KGF-2

KGF-2 is a member of the FGF family of mitogens. It has a highly selective action on epithelial cells. In addition to promoting re-epithelialization by a direct effect on keratinocytes that causes them to proliferate and migrate, KGF-2 may also stimulate granulation tissue formation by a direct chemotactic effect on fibroblasts [29,30]. It was found to be more effective than either the vehicle control or KGF-1 at closing the interstices of human meshed skin grafts explanted to athymic “nude” rats [31].

Following a phase-1 clinical trial to demonstrate safety when applied topically to skin, a truncated form of recombinant human KGF-2 (repifermin) was used in a phase-2a clinical trial in patients with venous stasis ulcers [29]. A randomized, double-blind, parallel-group, placebo-controlled multicenter study compared either placebo or repifermin (20 μg/cm² or 60 μg/cm²) applied topically twice per week for 12 weeks. A significant difference (P = 0.047) was seen between the combined KGF-2 treated groups and the placebo group for subjects who achieved at least 75% healing. The treatment effect appeared greater for ulcers less than or equal to 15 cm² in size and less than or equal to 18 months in duration. For this subgroup, differences were statistically significant for both the 90% combined healed group (P = 0.028) and the 75% combined healed group (P = 0.007) [29]. This trial was only 12 weeks in duration and presently a large multicenter trial is being conducted of longer duration and with a larger concentration of KGF-2.

EGF

The EGF family comprises four mammalian proteins: EGF, TGF-α, amphiregulin, and heparin-binding EGF [13]. Although EGF and TGF-α consistently stimulate the processes in vitro that are required for wound healing, topical treatment with these cytokines in acute and chronic human wounds in vivo has not been consistent [13]. The first clinical trial of any
recombinant cytokine growth factor to accelerate healing was the application of EGF in Silvadene cream (1% silver sulfadiazine) (King Pharmaceuticals, Johnson City, TN.) to split-thickness skin graft donor sites in burn patients [32]. The control group received Silvadene alone. The study showed a statistical difference of 1-day to 2.5-days in healing acceleration, which was not thought to be of clinical significance [4,13]. A crossover study of nine patients with various chronic wounds treated with Silvadene followed by recombinant EGF was subsequently reported [33]. The numbers were small, and the study design was not optimal; however, none of the nine patients healed while on Silvadene cream alone and eight out of nine healed on the Silvadene-EGF regimen [4]. This study is difficult to interpret because of the multiple etiologies of the wounds and the various healing processes involved [13].

**TGF-β**

TGF-β exists in at least three isoforms (TGF-β1, TGF-β2, and TGF-β3). The three have many similarities in stimulating collagen synthesis [4]. Animal studies suggest that TGF-β3 may have greater anti-inflammatory properties and may inhibit scarring [34]. Two studies have been reported utilizing TGF-β2 in a collagen sponge vehicle for the treatment of chronic venous stasis ulcers [35]. A preliminary open-label trial using 0.5 μg/cm² of TGF-β2 applied three times a week for 6 weeks showed that the open area of the ulcers treated with TGF-β2 had decreased by 73%, whereas the area of the placebo-treated ulcers had increased 9%.

This trial was followed by a prospectively randomized, blinded, placebo-controlled three-arm trial comparing 2.5 μg/cm² TGF-β2 in a lyophilized collagen sponge vehicle, the collagen sponge alone, and a standardized care dressing [35]. Again, the ulcers treated with TGF-β2 responded better, decreasing by 57% compared with 30% for collagen sponge alone, and 9% for the standard dressing.

TGF-β2 has also been used to treat diabetic neuropathic ulcers. In a blinded study using three doses of TGF-β2 (0.05, 0.5, and 5.0 μg/cm²), each demonstrated a higher rate of healing than did the vehicle control [36].

**Granulocyte-macrophage colony-stimulating factor**

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a hematopoietic growth factor that can stimulate leukocyte, macrophage, keratinocyte, and fibroblast activity [4,13]. It has been used topically for nonhealing abdominal wounds following cancer surgery [37], and injected perilesionally in two clinical trials by daCosta et al [38,39] to accelerate the healing of venous stasis ulcers.

In the first trial of 25 patients, ulcers received either 400 μg of GM-CSF in four perilesional sites as a one-time injection or similar placebo injections. Fifty percent of the GM-CSF-treated patients healed versus 11% of the placebo-treated patients [38]. A follow-up dose-ranging trial compared 200 μg with 400 μg GM-CSF administered weekly for 4 weeks in 60 patients. The complete healing responses were 57% and 61% for the 200-μg and 400-μg groups compared with a 19% response for the placebo group (P = 0.014) [39]. Other trials have found a significant complication rate when GM-CSF was injected perilesionally.

**Insulin-like growth factors**

This family of proteins includes insulin-like growth factor (IGF)-I and IGF-II, which have been studied in vitro and in preclinical studies of wound healing. Also known as somatomedins, they show significant amino acid homology with insulin [4]. IGF-I is important in promoting protein synthesis and increases the proliferation of many cell types, including fibroblasts [13]. Although there have been several preclinical studies suggesting that IGF-I and IGF-II might enhance wound healing processes, no clinical trials have been reported. The action of growth hormone may be through the activation of IGF-I, however, and recombinant human growth hormone (rHGH) has been used in a double-blind placebo-controlled trial of 37 patients with chronic leg ulcers [40]. The patients were randomized to receive either 1 IU/cm² ulcer area of topical rHGH or placebo, in addition to “standard” treatment (compression and hydrocolloid dressing). The healing rate was 16% per week in patients receiving rHGH compared with 3% per week in the placebo group [40]. With 18 out of 37 patients failing to complete the study, it is difficult to draw conclusions about this trial. Because it is postulated that the effect of rHGH might be due to a rise in IGF-I, possibly a trial with topical IGF-I would be more successful [4].

**IL-1β**

Recombinant IL-1β has several actions that contribute to wound healing, including chemotraction of cells (predominately neutrophils and macrophages) to the wound site, proliferation and fibroblast-induced release of collagenase-like activity, and stimulation of capillary endothelial cell proliferation [4,13]. It also
has the ability to stimulate monocytes and granulocytes and stimulate macrophages to produce other growth factors [41]. A prospective, randomized, double-blind, placebo-controlled trial that included 26 patients with pressure ulcers who were treated with either 0.01 μg/cm², 0.10 μg/cm², or 1.0 μg/cm² of recombinant human IL-1B or a placebo vehicle demonstrated no statistical differences among the four groups [41]. Patients who received the highest dose of IL-1B showed different in vitro fibroblast characteristics than did patients in the other groups, however. Fibroblast “senescence” seemed to be overcome after 28 days of treatment with IL-1B at 1.0 μg/cm²/d. Despite preclinical studies suggesting that exogenous IL-1B might shift the wound trajectory to the left, the attempt in pressure ulcers was possibly ill conceived because increased levels of proinflammatory cytokines are thought to be part of the pathobiology of wound chronicity [4,8].

Combination of cytokine growth factors

If a single cytokine growth factor does not establish efficacy in manipulating healing in the chronic wound, the possibility of combinations or sequences of growth factors exists, and are nearly endless [4]. Several preclinical examples of this exist [13]. A small multicenter clinical trial of combined topical PDGF and IGF-1 for enhancement of diabetic foot ulcer healing did not show clinical efficacy [4]. The idea of combining growth factors for topical application to wounds is the concept behind the autologous platelet releasate—platelet-derived wound-healing formula (PDWHF). This releasate from autologous platelets contains PDGF, TGF-β, platelet-derived angiogenesis factor, platelet-derived EGF, platelet factor-4, and other unknown factors [4]. A controlled, double-blinded, crossover trial of 32 patients has been reported in which 81% of patients treated with PDWHF had 100% epithelization after 8 weeks of treatment compared with only 15% in the control group [42].

At least five other trials have been reported using PDWHF on lower extremity ulcers [13]. Most were destined to fail due to a lack of homogeneous subgroups and various etiologies of leg ulcer that gave contradictory results [4]. When only diabetic neutrophil ulcers were carefully stratified and entered into a double-blind, multicenter trial, however, it was found that all three concentrations of PDWHF tested outperformed the saline placebo over a 20-week period [43]. Only 29% of the neutropenic diabetic ulcers achieved complete healing in the placebo group compared with 80%, 62%, and 52% in the 0.01, 0.033, and 0.1 PDWHF dilution-treated groups (P = 0.02) [43].

Sequential applications of growth factors

The availability and function of the various growth factors in normal wound healing appears to be sequential [4]. Platelet or inflammatory cell-released factors are present in the wound at an earlier time in the healing trajectory than are fibroblast-secreted factors. Based on animal experiments of wound contraction models, a large trial investigating the sequential topical application of GM-CSF followed by bFGF in pressure ulcers was conducted [44]. The trial demonstrated that sequential therapy was successful in shifting the healing trajectory to the left, but this particular sequence choice was not as effective as bFGF alone [44].

The most interesting part of this study was the long-term follow-up results of these patients [45]. Of the patients healing greater than or equal to 85% during treatment, 84.6% were 100% healed after 1 year compared with 61% of those that healed less than 85% during treatment (P < 0.05). Because only patients receiving exogenously applied cytokines achieved greater than 85% closure during the treatment phase of the trial, the excellent long-term outcome appears attributable to the cytokine therapy [45]. Long-term outcome was better in this growth factor trial than with surgical or standard nonoperative treatment of pressure ulcers [45,46].

Combinations of growth factors and antiproteases

If a single growth factor, a combination of growth factors, or a sequence of growth factors topically applied do not eventually prove successful in enhancing healing of the chronic wound, it may be due to the pathobiology of the wound demonstrates that an imbalance of the synthetic-degradation equilibrium of the extracellular matrix [4,5]. In chronic wounds, there is an excess of MMPs and a decrease in their natural inhibitors, tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2). Not only are the degradative MMP enzymes elevated but cathepsin G, elastase, and urokinase are elevated as well [7]. Because all of these could theoretically degrade exogenously applied growth factors, it has been suggested that one could treat the chronic wound with natural or synthetic exogenous protease inhibitors, induce expression of endogenous antiproteases, or attack the excess neutrophil accumulation responsible for much of the protease excess [7]. To re-establish the wound-healing trajectory uniformly in chronic wounds, it is possible that cytokines and protease inhibitors may require simultaneous administration [4,5,7,11]. Although this approach has not
yet been reported in clinical trials, ointment containing EGF and a serine protease inhibitor has been tested in open rat wounds and showed improved healing [13].

Attempts to manipulate healing of acute wounds with cytokines

Even when tissue repair is efficiently activated following injury and reliably passes through the tightly orchestrated cellular and molecular healing pathways of the wound-healing scheme, the resultant “normal” healing trajectory requires a significant amount of time [4]. Patient morbidity occurs with what is labeled “normal” healing. Acute burns are an obvious example, but all soft tissue injuries are similarly debilitating. When acute healing is delayed or incomplete, a surgical complication is the result [4]. When acute wounds fail, they result in dehiscences, incisional hernia formation, gastroenteric fistulae, vascular anastomotic leaks, bronchopleural fistulae, and luminal stricture formation [4]. Because of these problems, newer data are emerging using these cytokines for acute wounds that are healing with a “normal” trajectory. The goal of these attempts is to change the timing of cytokine action to shift the normal trajectory farther to the left, toward “ideal” healing.

Acute burns

Thermal burn injuries are examples of wounds whose acute healing time course can be prolonged. If the burn is deep, the wound is excised and a skin graft is immediately applied. The healing is then timely and orderly, resulting in a sustained anatomical and functional result. This fulfills the definition of acute wound healing [1]. When the burn wound is more superficial, however, the time to epithelialization is prolonged.

Application of a cytokine to accelerate burn wound healing has recently been attempted. A clinical trial encompassing 600 patients from 32 hospitals across China investigated the efficacy of topical bFGF to enhance the healing of partial-thickness second-degree burns [47]. This study used the gold standard of histological diagnosis of depth of burn and divided the patients into superficial and deep partial-thickness burns. Superficial and deep second-degree burns treated with recombinant bFGF healed in a mean of 9.9 ± 2.5 days and 17.0 ± 4.6 days, respectively, compared with 12.4 ± 2.7 days and 21.2 ± 4.9 days for the placebo groups. The significance was $P = 0.0008$ for the superficial partial-thickness burns and $P = 0.0003$ for the deep partial-thickness burns [47]. Another attempt to accelerate wound healing in burns has been the application of cytokines to accelerate closure of interstices of meshed split-thickness skin grafts. This has been successful in an animal model for KGF-2, bFGF, and TGF-β2 [48].

Surgical incisions

Realizing that the sigmoid-shaped curve of gain in breaking strength or tensile strength is a compromise, attempts have been made to shorten the inflammatory or lag phase of healing, accelerate the proliferative phase of healing, and modulate the remodeling phase of healing [4]. One approach for accelerating the inflammatory/lag phase of wound healing is to therapeutically activate the target tissue prior to wounding. “Priming” early acute wound healing using classic wound repair cytokines such as PDGF, GM-CSF, and IL-1β has been shown to preactivate the humoral and cellular elements of acute tissue repair and to accelerate the recovery of tissue-breaking strength following incision [49]. The priming approach induces chemotaxis of regulatory cells important to tissue repair into the planned incision site [4]. Because activated cells such as macrophages and fibroblasts are capable of synthesizing and releasing additional cytokines and are under the feedback regulation of the acute wound milieu, an in situ approach such as priming is theoretically appealing [4].

A second strategy for inducing an acceleration of the acute wound-healing trajectory is to stimulate the proliferative phase of acute tissue repair molecularly. TGF-β3 was the first tissue cytokine growth factor used to shift the proliferative phase of incisional healing to the left successfully and accelerate the recovery of wound tensile strength [50]. Other tissue repair growth factors such as PDGF, bFGF, and TGF-β2 have since shown similar promise following acute injury [49,51]. In all of these preclinical studies, dermal wounds were treated at the time of incision and an acceleration of the acute healing curve again was observed.

The majority of preclinical and clinical studies of acute tissue repair has focused on the dermis. This is true despite the fact that the complications of acute wound failure clearly cross the boundary of dermal wound failure and are focused on the fascia [4]. To compare fascial healing to the information available for dermal healing, a novel animal model has been developed to compare simultaneous ventral abdominal wall dermal and midline fascial (linea alba) incisions [21]. By isolating the healing dermal and fascial incisions, it was possible to observe that the
fascial wound regained breaking and tensile strength significantly faster than did the dermis [4,21]. Isolated fascial fibroblasts were also more active than were dermal fibroblasts in vitro, as measured by fibroblast proliferation and fibroblast-populated collagen lattice contraction [21]. It was then hypothesized that the steeper slope of the fascial healing trajectory may be more susceptible to an acute wound-healing insult and possibly susceptible to cytokine manipulation. This hypothesis has proven to be true. Major extirpative surgery, such as a partial hepatectomy, decreases the fascial gain of tensile strength in the surgical incision. This decrease in tensile strength gain can be reversed by application of TGF-β2 at the time of fascial wound closure [52]. Similarly, in an animal model of incisional hernia, both bFGF and TGF-β2 were able to restore defects in fascial healing [53,54]. In fact, TGF-β2 injected into the fascia at the time of incision totally prevented hernia formation [54].

None of these approaches have been attempted clinically. Questions that need to be answered before clinical usage include the determination of appropriate doses to induce optimal acute tissue repair, and whether a specific combination and or sequence of acute tissue cytokine therapy will result in improved outcomes. A reliable manner for cytokine delivery to acute wounds also remains a problem, as does the effect of cytokine therapy on nondermal wounds [4]. Once these issues are resolved, however, earlier induction of the components of acute tissue repair may shorten the time required along the healing continuum [4].

Explanation for limited success of wound manipulation by cytokines

To date, a single growth factor, PDGF-BB, has been approved by the USFDA for topical use to enhance wound healing, and this approval has been limited to a single wound type. Although overall this appears discouraging, many individual clinical trials have been encouraging [20]. How does one reconcile this apparent contradiction? First, attention must be paid to the caveats published for the design of clinical trials [20]. These include not adequately controlling factors such as bacteria, ischemia, and hypoxia that are known to inhibit the various wound-healing processes [13,20]. Also, because various growth factors affect different processes of wound healing and the degree to which any single process plays a part in the repair of a given wound is variable, it is clear that individual growth factors should be targeted at those specific processes that a given wound uses to heal [4,20]. If all of the caveats had been considered and included in cytokine clinical trial design, it is possible that more dramatic outcomes would have been achieved for wound-healing enhancement [4]. These caveats, however, have not always been considered in the trials reported to date. When trials have attempted to be careful in enrolling homogeneous subgroups by restricting etiology, transcutaneous partial pressure oxygen levels, and bacterial loads, results have often been much more favorable [4,13].

The number of growth factors that affect the various processes in the wound-healing cascade are considerable. Because animal models have not been particularly helpful in predicting effective human doses, the attempts to find the correct factor, administered at the correct time, the correct dosage has been, and will continue to be, very difficult [13]. It may be that attempting to manipulate the wound with cytokines by applying them topically as discussed in this article will not prove to be the most effective approach. Gene therapy may prove to be a more targeted approach to using cytokines. Gene therapy uses DNA as a superpharmaceutical agent to alter cell function for an extended period of time in relation to more established direct delivery systems [55]. Although gene therapy for wound healing is not yet a reality for true utility, recent preclinical experiments suggest that it may prove to be effective [56,57].

Summary

Most individuals expect that healing is an inevitable outcome; wound healing is taken for granted [18]. Although wound healing is perceived as inevitable, it can be fraught with problems and altered at many points [4]. In the past, optimization of wound healing focused on minimizing contamination, accurate tissue approximation, and providing protection. With the advent of recombinant technology, optimization can now include manipulation of the molecular and cellular wound environment. Although the exact manipulative scheme has not yet evolved, it is clear from the multiple attempts reported in this article that understanding and progress is being made.

References


