Growth factors in wound healing

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The repair of wounded skin commonly is divided into three broad phases (although there is considerable overlap): (1) inflammation, (2) proliferation, and (3) remodeling. Each step during the process is orchestrated by varying levels of many growth factors and by differential expression of their receptors. Growth factors are the engines, or modulating factors, that drive wound healing. Through their induction of chemotaxis (attracting cells into the wound) and cell proliferation and by stimulating cells to upregulate protein production, they determine extracellular matrix (ECM) synthesis, matrix turnover, and cell death. The response to growth factors in the wound environment is augmented by their ability to act on cells in an autocrine fashion [1]. During the proliferative phase of wound healing, there is a rapid and dramatic amplification of cellular activity secondary to growth factors stimulating the cells from which they are released.

The large alphabet soup of growth factors that is created during wound healing results from the facts that almost every cell type present in skin is involved in growth factor production to some degree and that some cells release many different growth factors in varying ratios during the process. Platelets release large amounts of platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-β and smaller amounts of insulin-like growth factor (IGF), epidermal growth factor (EGF), and TGF-α. Fibroblasts produce some of the same growth factors and vascular endothelial growth factor (VEGF); fibroblast growth factor (FGF) isoforms 1, 2, and 7 (FGF-1, FGF-2, FGF-7); IGF-1; IGF-2; and a variety of interleukins, interferons, and colony-stimulating factors. Blood-borne monocytes reach the wound and differentiate into macrophages. Macrophages are activated and become the most important overall producers of growth factors and cytokines during wound healing. They may produce 100 proteins...
that are active in stimulating cell migration, proliferation, matrix synthesis, and autocrine production of growth factors. Keratinocytes, endothelial cells, perivascular cells, and plasma add growth factors to the wound healing milieu, and almost every cell is affected in some way by the presence of growth factors [2].

The underlying rationale for growth factor therapy is the supposition that in problematic and chronic wounds, the production of one or many is suboptimal. By adding more of a growth factor that is lacking or by giving the surrounding tissue the ability to upregulate its own production, it is hoped that a positive effect on healing would be seen.

**Inflammatory phase**

When the integrity of human skin is broken and capillaries and other vessels are sheared, there is an extravasation of blood and blood products into the site of disruption. Here, blood coagulates and platelets aggregate, forming a fibrin-rich plug. This plug helps prevent further loss of blood from vessels and forms a barrier against contamination from invading microbes. It also marks the first stage of tissue repair in that it serves as a provisional matrix, a foundation on which wound healing can take place.

In the wound bed, during the initial stages of inflammation, damaged parenchymal cells, platelets, and activated complement pathways produce vasoactive mediators. These mediators, along with histamines and leukotrienes that are released from local mast cells, cause endothelial cell changes leading to the attraction, adherence, and passage of leukocytes between endothelial cells and into the region of tissue damage [3]. In addition to vasoactive mediators, platelets release growth factors, such as PDGF, TGF-β, FGF, and EGF, which orchestrate the early chemotaxis and activation of cells involved in wound healing [4]. Neutrophils “clean” the wound by phagocytosing damaged and dead tissue and foreign debris and by using their toxic oxygen products to destroy microbes. In the absence of bacteria or necrotic debris, the expression of granulocytic signaling factors is transient, after which many neutrophils, which have a limited life span, are phagocytosed by macrophages whose entrance into the wound and activation is controlled by a growing number of growth factors. The remainder of the neutrophils are trapped in the quiescent eschar and shed when the eschar sloughs away.

Shortly after clot formation, and within a few hours of wounding, epithelial cells begin to migrate from the wound periphery and onto the exposed tissue in response to growth factors, such as EGF, TGF-α, TGF-β, granulocyte-macrophage colony-stimulating factor, and the FGFs [5–8]. These growth factors induce the epithelial cells to shed their cell-cell adhesion proteins and migrate either under the eschar (if desiccated) or over the provisional fibronectin/fibrin matrix to cover the wound.
Proliferative phase

In contrast to neutrophils, monocytes, in response to monocyte-specific chemoattractants, continue to migrate into the wound long after the initial stages of healing. When present in the tissue, they become activated to macrophages. These macrophages begin producing their own growth factors, including PDGF, TGF-α, TGF-β, IGF-1, VEGF, and tumor necrosis factor (TNF)-α [2,9], which, along with the growth factors produced by damaged parenchymal cells and the stored growth factors that are released by stimulated platelets, orchestrate the proliferative phase of wound repair. This phase is carried out within the fibrin provisional matrix and is aided by the presence of fibrin, fibronectin, collagen, and hyaluronic acid. These extra-cellular proteins and molecules allow for cell guidance through the wound in the case of the former three and low impedance to mobility in the latter [10]. Fibroblasts invade the wound and begin to lay down new matrix mainly in the form of collagen and glycosaminoglycans. Concurrently, neo-vascularization begins to take place [10].

Remodeling phase

The final stage of wound healing begins while tissue proliferation is still occurring. Reduced concentrations of growth factors involved in earlier phases of wound healing and the increased expression of others, including high levels of TGF-β1, initiate the differentiation of fibroblasts into myofibroblasts, cells that contain increased numbers of actin filaments [11]. The importance of these cells stems from their contractile ability. The lattice-like structure of the newly deposited ECM is responsive to the contractile forces of activated myofibrils, allowing contraction to play an important role in wound closure. The new environment also causes epidermal cell differentiation and adhesion, which reestablishes the impermeable surface barrier of the skin.

Apoptosis begins during the remodeling phase of wound repair, first with endothelial cells and then myofibroblasts, leaving a relatively acellular scar. The signals for the remodeling phase are still largely unknown, but blocking TGF-β activity has been implicated in excessive scarring [10,12], suggesting it may play a role in halting scar formation by encouraging cell apoptosis.

Growth factors

There are five known superfamilies of growth factors. The growth factors, along with their receptors, vary in structure and cell pathway activation between families and within each family. Still, some consistencies exist. Most growth factors originate from large proteins or multiple gene products and undergo posttranslational modification before being released in an active state [13]. Growth factor receptors are transmembrane glycoproteins whose effects are seen largely through kinase domains and phosphorylation reactions.
The PDGF superfamily of growth factors comprises PDGF and VEGF. These two proteins are similar in structure but bind to different receptors and have different cellular effects. The effect of PDGF stimulation is seen in cells of mesodermal origin, whereas VEGF has its primary effect on endothelial cells [13].

Originally shown to be a mitogen for fibroblasts, smooth muscle cells, and glial cells [14], PDGF is the first and, to date, only growth factor to be given US Food and Drug Administration approval for clinical use. It first was isolated from human platelets but since has been shown to be secreted from many cell types, including monocytes, macrophages, fibroblasts, smooth muscle cells, and endothelial cells. In vitro studies have shown that PDGF stimulates chemotaxis, proliferation, and new gene expression in these cells [15]. It is known to exist in five isoforms: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. They result from the heterodimerization or homodimerization of four gene products, the A, B, C, and D chains [16–18]. Although the heterodimer PDGF-AB is the predominant product in human platelets, porcine platelets contain the BB homodimer, and the B chain is the normal cellular form of the protein product of the v-sis oncogene. As a result, early animal studies and clinical trials using a recombinant human form have focused primarily on the efficacy of PDGF-BB in wound healing [15].

PDGF plays a key role throughout the wound healing process. Over the first several days after an injury, its release from platelets and endothelial cells allows for directed and sequential migration of neutrophils, macrophages, and fibroblasts into and around damaged tissue. When at the wound sight, continued stimulation of the newly arrived cells by PDGF results in endogenous production of the growth factor and provisional ECM synthesis, fibroblast proliferation, and eventually collagen production. This stimulation continues for 2 to 3 weeks, after which PDGF contributes to the remodeling of the wound by helping to orchestrate active collagen turnover and cross-linking [15].

Individual growth factors do not work alone, but rather their effect is determined by their relative concentration to other growth factors in the area [15]. The change in PDGF’s influence on cells, from one of chemotaxis and proliferation to that of collagen and ECM production, occurs as a result of the varying amounts of many factors, including IGF-1, interleukin-1, EGF, TNF-α, and most importantly TGF-β [2,15,19,20].

Because of its ability to enhance the cellular response to a wound and to contribute to collagen production, it was speculated that the exogenous application of PDGF could amplify this effect through the autocrine feedback loop. Early animal studies supported this claim. Treatment of incisional wounds in rats with a single dose of recombinant human PDGF produced an increase in the inflammatory response, wound cellularity, granulation tissue formation, neovascularization, and rate of epithelialization over normal control wounds [21,22]. One study found an increase in
breaking strength of 150% of normal control wounds and showed that wound healing was accelerated 10 days between 2 and 7 weeks postwounding. As wounds matured, the gap in healing rates narrowed so that by 89 days postwounding, no difference was seen, suggesting that the effect of a single dose is long lasting and beneficial, but transient [22]. Nonetheless, the remarkable impact of a single topical application at the time of wounding and the absence of a deleterious effect on scarring suggested that PDGF was a highly promising candidate for therapeutic testing.

The initial human trials with PDGF were pursued in pressure sores. A phase I study [23] later was expanded to a phase II study [24] using PDGF in a saline vehicle over 1 month. It indicated efficacy in accelerating the rate of closure of pressure sores. Phase III studies were never published, however, suggesting that success was not reached in larger studies that followed the wounds to complete healing. To date, no large clinical study has shown efficacy for any therapeutic agent in the treatment of pressure sores, although many have been conducted. As discussed later, PDGF trials provided an early indication as to the enormous challenge researchers would face when conducting clinical studies in chronic wounds, specifically pressure sores. The heterogeneity of these wounds and the existence of multiple intercurrent factors have profound effects on healing rates and often overwhelm any treatment effect.

Other studies focused on the efficacy of PDGF in diabetic foot ulcers. An initial multicenter phase II study led by Steed [25] indicated that the number of patients who went on to heal completely over the 20-week duration of the trial doubled in the treatment group compared with controls. Three pivotal phase III trials were conducted [26–28]. They led to the approval by the Food and Drug Administration in 1997 for use of the growth factor in this restricted patient population. The approval process involved more than 1000 patients in trials conducted over 7 years. When the results from all phase III trials were combined, with no exclusions, PDGF gave a persistent 10% overall increase in the rate of complete healing. Although a modest improvement, given the consequences of limb amputation in treatment failures for diabetic ulcers, it should not be understated.

The healing rate of treatment and control groups varied by 10% or more between each trial in the diabetic ulcer study. In one of the three large pivotal trials, the treatment effect of PDGF failed to reach statistical significance (although a trend was present), suggesting inherent variability of the testing process and underscoring the need for precision when designing and carrying out testing for the treatment of chronic wounds. Most companies have made decisions on whether to pursue clinical trials with growth factors based on much smaller groups of patients. If the variation in results between centers in PDGF trials is any indication, in many cases, these companies may have concluded prematurely that there was no therapeutic benefit to their particular growth factor because they did not examine the growth factor in enough patients or at enough centers.
Along with the difficulty in teasing out the inconsistency of data coming from small studies or between two studies with slightly different designs, experiences with PDGF in clinical trials showed that there are many potential pitfalls in the treatment of chronic wounds with exogenous growth factors. This may be why, with the exception of PDGF, basic science theory and successful animal studies have not translated into clinical application and why the clinical success of PDGF has been questioned by some. As stated earlier, wound healing is complex, incorporating coagulation, inflammation, angiogenesis, matrix production and deposition, remodeling, and cellular apoptosis into a dynamic process that is determined in large part by growth factor expression. The degree to which any one process (and its corresponding growth factor levels) plays a role in wound healing is variable spatially and temporally, bringing into question the benefit that would be seen after adding just one growth factor. The temporal effects of growth factors are crucial, yet the delivery methods and timing of growth factor therapy have not been sophisticated. Most trials have used growth factors in a simple vehicle with brief exposures of the wound to the growth factor. Because growth factors are taken up and often degraded or inactivated rapidly, there is good reason to believe that the benefits of individual growth factors have been missed by misguided or poorly designed studies that do not take these considerations into account.

PDGF’s success may be due in part to its resistance to proteases and the use of the agent in an appropriate patient population. It is known to be a stable protein. Eight cysteine residues per polypeptide chain, each linked by a disulfide bond, confer resistance to changes in heat and pH and to the effects of proteases [15], making it a good substance for introduction into a hostile, matrix metalloproteinase–rich environment. For this reason, despite success only in treating diabetic foot ulcers, PDGF studies continue for other chronic wounds, including chronic pressure ulcers.

Another growth factor that has been tested extensively for the eventual use in diabetic and pressure-related ulcers is TGF-β. Existing in multiple isoforms with receptors on most cells in the human body, TGF-β always has had great promise as a prototypic agent for improving wound healing. It is known to increase matrix deposition and wound contraction, as shown in animal studies [29,30].

TGF-β also has significant effects on modulating inflammation when given systemically [31], which has been a concern for researchers during the few clinical trials to date. However the safety margin of topical application has been quite high, so research into its use in wound healing has continued without fruition of this concern, so research into its use in wound healing has continued without fruition of this concern.

A phase II trial has shown that treatment with TGF-β₂ improves the healing rate of diabetic foot ulcers [32]. TGF-β₃ was used in a large phase III trial for pressure sores, sponsored by Novartis, but the results apparently
were disappointing and not published. TGF-β₁, which is the predominant isoform in wound healing, has never been tested in clinical trials.

The fact that it has been difficult to see improvement in pressure sore healing with the application of growth factors such as PDGF and TGF-β is not surprising. Along with the inherent difficulties that face any growth factor trial, as discussed previously, pressure sore trials are complicated further by compliance issues with pressure relief and wound care. The underlying cause of pressure ulcers is a loss of the ability to make frequent postural changes; most patients are incapable of providing their own pressure relief. When trying to heal a pressure ulcer, a single episode of sustained pressure or repeated incontinence can more than offset several weeks of optimal care. Similar to many chronic wounds, pressure sores often occur in the elderly. Many of these patients possess vascular pathology that results in ischemic wounds, further compromising wound healing.

In 1999, the authors showed that although exogenous TGF-β increased wound healing by new granulation tissue formation and reepithelialization in ischemic and nonischemic wounds in young rabbits, it had little effect on the wounds of aged rabbits and even less on the wounds of aged, ischemic rabbits [33]. The authors hypothesized further the lack of response in the aged group of ischemic wounds to be due to loss of expression or function of a components of the TGF-β signal transduction cascade. In vitro studies on keratinocytes support this hypothesis [34]. Most preclinical studies have been done in young animals in acute wounds with a good supply, which explains the potential limitations of these studies in translating to clinical success.

The idea of a poor blood supply being related to delays in wound repair led researchers to look at the role of VEGF in wound healing. Because it is known to promote angiogenesis, VEGF may benefit wounds suffering from an ischemic environment. Although similar to PDGF in amino acid sequence, sharing 24% homology with the PDGF-B chain [35], VEGF binds to different receptors and has significantly different action [1]. Five VEGF isoforms are generated as a result of alternative splicing from a single gene [36]. These isoforms bind to two VEGF receptors, found almost exclusively on endothelial cells [37,38], where they act as a potent mitogen, stimulating angiogenesis. In contrast to PDGF, VEGF does not act on macrophages, fibroblasts, or smooth muscle cells.

Although VEGF has little direct effect on most of the cells in skin, many cells either produce it or release factors that regulate its expression. FGF-4, PDGF, TNF-α, IGF, and some interleukins potentiate VEGF production, whereas other interleukins inhibit its release [36]. Nitric oxide released from cells enhances the effects of VEGF on blood vessels, and hydrogen peroxide that is released from invading neutrophils inactivates the growth factor. Keratinocyte growth factor (KGF), which is highly expressed after a dermal wound, stimulates VEGF production. Blood vessels respond to higher VEGF levels with vasodilation and increased permeability, and neovascularization
begins to take place in its presence. In normal wound healing, the magnitude of this response is controlled tightly by the other growth factors present in the wound and by molecules such as nitric oxide and hydrogen peroxide [36,39]. This control ensures that neovascularization occurs when necessary, to bring in material for wound repair, but that later, when this material is no longer needed, the new vessels regress.

As a result of its angiogenic properties, initial interest in VEGF centered on its role in highly vascularized tumors. More recently, animal studies and a few clinical trials have shown promise for the growth factor as a treatment strategy for patients with arterial disease, such as patients with ischemic myocardium and ischemic limbs [40]. VEGF has been studied as a treatment for improving skin flap survival. Studies on anterior abdominal skin flaps show increased survival when treated with VEGF in the protein, cDNA, or transfected form [41]. More recently, animal studies have shown that VEGF doubles granulation tissue formation in ischemic wounds in the rabbit [42]. No data currently exist, however, to suggest that in humans when given topically either as a protein or in an expression plasmid or recombinant virus, it has clinical benefit in wound treatment. Clinical applications may be restricted by the fact that VEGF does not influence directly epithelialization, matrix deposition, or wound contraction. Its role may be limited to situations in which ischemia is a factor in tissue survival, such as during tissue expansions in which skin often breaks down in regions of compromised blood supply [43]. Because of its limited activity in the wound healing system, VEGF is not likely to benefit wounds that present with specific pathologic causes, such as poor reepithelialization of damaged tissue. Potential exists, however, for its use as an adjuvant to other growth factors whose benefits are masked by the ischemic nature of a wound.

KGF is the most potent mediator of keratinocyte proliferation and motility and has substantial potential for increasing healing in chronic wounds whose cause is based in part on lack of epithelialization. In addition, either through direct influence or by indirectly stimulating keratinocytes to release other growth factors, a beneficial effect of KGF has been shown on the production of granulation tissue in animal models [44]. This member of the FGF family of growth factors is expressed weakly in normal human skin but is strongly upregulated in dermal fibroblasts after tissue damage. Keratinocytes express a high-affinity receptor for KGF and show a robust response to its presence, upregulating the expression of many genes. These genes not only cause the cells to produce VEGF, as stated earlier, but also they lead to keratinocyte mitogenicity, differentiation, and migration over the wounded area. An added effect of receptor activation is the intracellular production of glutathione peroxidase, a DNA repair enzyme that helps protect keratinocytes from a growing number of reactive oxygen species released into the wound to destroy foreign material [45].

KGF-2 (57% homology with KGF-1) has been shown to increase granulation tissue formation by directly stimulating the migration of
fibroblasts into wounds. Animal studies using KGF-2 (Repifermin, Human Genome Sciences, Gaithersburg, MD) showed a dramatic increase in granulation tissue formation and wound healing in an ischemic rabbit ear model in young aged animals, the latter being a result not found using KGF-1 [46]. A multicenter, double-blind study using recombinant KGF-2 in venous ulcers reported that 90% to 100% healing was seen in twice as many patients in the treatment group as in the control group at the end of 12 weeks and that the percentage of healing in the treatment group was double that of controls over the same period [47]. An important side note is that, similar to results seen in PDGF treatment, treatment with exogenous KGF does not lead to hypertrophic scarring. This finding contrasts with the persistent hyperplasia seen in the pathologic conditions that are thought to involve KGF, such as psoriasis, and suggests that there is no long-term risk of increased scarring as a result of using the growth factor in a therapeutic setting [45].

Treatment strategies

The reason for the disappointing results in growth factor clinical trials to date is undoubtedly multifactorial. The success of recombinant PDGF-B in the form of becaplermin (Regranex) cannot be overlooked, however, given the severity of the problem of diabetic ulcers and the conclusiveness of the large clinical trials. This study has set the standard for clinical trials of growth factors in wound healing and should make it easier for researchers in the future to create a suitable study design and ultimately to have successful outcomes.

One finding of the Regranex study was that standardizing wound care during a clinical trial of growth factor efficacy is important. While analyzing the data from the trial, the discrepancy in wound healing that was seen between different centers was examined. It was found that compared with the centers where débridement was performed less frequently, the care facilities where débridement was more routine (perhaps a surrogate marker for quality of care) had a greater amount of healing in the treated wounds compared with control wounds in the same patient. If all facilities were standardized to the highest level of wound care, the 10% treatment effect seen while using Regranex might have been more than doubled, more closely approximating the 25% treatment effect seen in the phase II trials.

Another issue that requires attention when constructing a study design is the vehicle that will be used to deliver the growth factor. To date, all clinical trials have been performed with a simple vehicle that does not provide sustained release. It has been shown that sustained release of growth factors leads to a superior outcome. Doukas and colleagues [48] showed that a collagen matrix gel is superior to saline in localizing and prolonging the effects of PDGF in dermal wounds.

The authors have described wound healing as a process that is affected by a complex milieu of mediating substances, with an orchestrated release of
multiple growth factors varying in temporal expression and concentration. The postulation has been that, because of these wound healing dynamics, the application of a single growth factor to aid in the healing process is not optimal and that some growth factor studies probably have failed for this reason. It is also true, however, that the individual expression of many of the growth factors found in wound healing indirectly leads to expression of multiple growth factors through activation and stimulation of macrophages and other cells that express these growth factors. There is still great value in studies looking at individual growth factors.

The hostile, protease-rich environment that has been well documented in chronic wounds has been mentioned [49]. One strategy to counteract this effect is to treat wounds with protease inhibitors. This is being tried in early clinical trials, but not yet in combination with growth factors.

Multifaceted strategies, such as combining growth factor therapy with activators of other signal transduction pathways (eg, hyperbaric oxygen, which results in reactive oxygen species), may potentiate the effect of growth factors. This hypothesis already has been substantiated in animal studies [50,51], and human trials are under way.

The strategy attracting the most interest in wound healing is the use of gene therapy. This technique for growth factor introduction takes advantage of a cell’s ability to produce its own proteins by introducing genes that code for a desired growth factor. The cell transcribes and translates this transgene as if it was its own, yielding increased protein product of the growth factor. The tremendous potential advantage of this technique is that a single gene transfection leads to several days of continuous expression of the gene with resultant protein production that can act locally before protease degradation.

The field of gene therapy is moving rapidly, and multiple strategies have been used for gene transfection in chronic wounds. In contrast to most other diseases being treated with gene therapy, by virtue of the fact that chronic wounds are cutaneous, they allow for gene therapy to be targeted locally as opposed to systemically. This local targeting results in a larger number of transfection strategies because the researcher is not limited by the concern for systemic toxicity.

Initially, low levels of gene expression were found when naked DNA simply was injected into a wound site using a syringe [52]. More recently, chemically mediated gene transfer, using liposomes or other carriers to introduce a gene into the nucleus of target cells, and electroporation, which employs an electrical field to induce cell membrane permeability, have been found to increase transfection rates and prolong gene expression in animal models [53,54].

Particle-mediated gene transfer originally was used for the introduction of genes into plant cells but since has been used to introduce PDGF successfully into diabetic foot wounds [55,56] and has shown some utility for other growth factors [57]. This technique couples DNA to microscopic gold particles. These particles are accelerated to a high velocity and directed into
the target cell. A variation of this method, called microseeding, involves coating solid needles with DNA of interest. A high-speed, oscillating instrument is used to introduce the transgenic material into cells, similar to how skin tattooing is performed. It has shown a threefold increase in protein yield over particle-mediated gene transfer and has the benefit of not introducing foreign material, such as gold particles, into the wound. It is also more accurate in determining the depth of penetration of the gene during gene transfection [57]. Although each of these methods lacks the transfection rates and sustained gene expression seen in viral transfection, another method for introducing genes into a cell, they share the common advantages of having lower toxicity than viral transfection and not requiring the use of an infectious agent.

When viruses are used for the introduction of growth factors into cells, a gene that codes for the desired growth factor replaces a viral gene. After the pathologic and replicative properties of the virus are disrupted, the vector and gene of interest are introduced into a wound. Viruses most commonly used in current transfection studies include retrovirus, adenovirus, adeno-associated virus, and lentivirus. Retrovirus and lentivirus transfect only dividing cells, and their insertion into the genome raises significant safety concerns. Adenoviral vectors offer the advantage of in vitro transfection rates approaching 100% and gene expression lasting several days. The adenovirus causes an immune response, however, which in animal models has caused a deleterious effect on wound healing when the virus has been applied to wounds [56,58]. Using adeno-associated viral vectors eliminates the need for concern over viral replication, but these vectors have not yet been used in animal models of wound healing. Despite these concerns, the potential of viral-mediated gene therapy seems good, given the magnitude of the effects that already have been seen in animal models [58].

**Future directions**

Chronic wounds are an ever-increasing problem. Approximately 1.5% of the population has a chronic wound at any given time [59], and this number will rise as medicine is able to support a growing number of aged and debilitated patients. Currently, most treatment strategies for chronic wounds employ techniques that have varied little over the course of the past century and that are relatively ineffective at bringing difficult wounds to a rapid closure. In the 1980s and 1990s, research on growth factors proved that they are an integral part of the normal wound healing response and that their absence or ineffectiveness can have a negative influence on the process of healing. A goal of numerous academic and industrial researchers is determining how manipulation of growth factor expression can achieve more rapid and normal healing. With new and improving methods of
delivering growth factors to a wound, focus now will turn to which combinations of factors are needed for the various forms of pathologic healing and at what levels their expression most would improve a patient’s ability to heal.

Recognizing this eminent need to regulate growth factors quantitatively and temporally, research is beginning to focus on the control of gene expression. This control can be achieved by coupling a growth factor gene with a promoter that is responsive to a pharmacologic agent. In this way, the timing and amount of growth factor expression are determined by the introduction or removal of the agent at different times throughout healing [60].

Ultimately, it is possible that customized treatment strategies will exist for the variety of chronic wounds that are seen. The first step is to understand the deficiencies and optimal concentrations of growth factors in each type of chronic wound. Finally, by using the various methods for the introduction and control of gene and protein levels, growth factors will be added to the wound healing milieu in the most beneficial way.

References


