Veterinary Surgery, 22, 6, 490–495, 1993

Wound Healing

The Role of Platelet-Derived Growth Factor and Transforming Growth Factor Beta

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Recent investigation into the mechanisms of wound healing has indicated the interaction of many substances, including several growth factors. The activity of platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β), are best defined. Both factors are secreted primarily from the alpha granules of platelets, but also from activated macrophages and fibroblasts. Investigation implicates the platelet as the initiator of wound healing, secreting PDGF, TGF-β, and other factors that are chemotactic for monocytes, macrophages, and fibroblasts. Although their mode of action and degree of effect are different, both PDGF and TGF-β increase the collagen content and early rate of gain of strength in wounds in normal and compromised tissue. In normal tissue, however, there is no long-term effect on wound outcome. The use of exogenous growth factors offers potential for chemical manipulation of the healing wound, particularly in tissues that are compromised, or where healing is abnormal.

INVESTIGATION OF THE physiology of wound healing has produced insights into the complex molecular mechanisms involved. This improved understanding of the process offers potential for exogenous manipulation of wound healing. A number of growth factors involved in wound healing have been identified, including platelet-derived growth factor (PDGF), transforming growth factors alpha and beta (TGF-α, TGF-β), epidermal growth factor (EGF), fibroblast growth factor (FGF), and insulin-like growth factor (IGF).[1,2]

Current theories suggest that platelets may initiate the healing process, which is then amplified or sustained by wound macrophages, endothelial cells, and fibroblasts.[1] Platelets initiate wound healing through the release of factors, including platelet-activating factor (PAF), PDGF, TGF-α and TGF-β.[1-3] Similarly, wound macrophages release PDGF, TGF-α, TGF-β and FGF.[2] This article reviews the biology of PDGF and TGF-β, their role in wound healing, and the effect of exogenous administration on wound healing.

Phases of Wound Healing

Wound healing is classically described in three phases: (1) the inflammatory and debridement phase that involves directed and sequential migration of neutrophils, monocytes, macrophages, and fibroblasts into the wound over the first two to five days; (2) the repair or proliferative phase that involves activation of wound macrophages and fibroblasts, resulting in endogenous growth factor production, extracellular matrix synthesis, fibroblast proliferation, and collagen synthesis during the subsequent two to three weeks; and (3) the maturation phase that involves remodeling of the wound with active collagen turnover and cross-linking from two weeks to one year.[4-6]

Inflammation

Platelet activation. The inflammatory response is essential for the repair and restoration of the structure and function of damaged tissue. The platelet is the first cell at the site of injury, appearing almost immediately, coincident with hemorrhage.[1] The loss of the endothelial integrity of the vessels during tissue damage results in exposure of type IV and V collagen in the subendothelium. This promotes aggregation and binding of platelets to these structural proteins and results in platelet activation.[7] Activated platelets undergo a series of structural and functional changes involved in coagulation.[7] In addition, the platelet secretes a number of factors including serotonin,

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fibronectin, adenosine diphosphate, thromboxane A_2, platelet factor 4, PAF, and PDGF.[7]

Chemotaxis. The local release of chemotactic factors signals neutrophil migration and initiates the process of diapedesis (migration) between endothelial cells. This is enhanced by increased capillary permeability after the release of several vasodilator substances in the wound, including serotonin, histamine, bradykinin, and arachidonic acid metabolites. Platelet factor 4 (PF4, an alpha-granule protein) is released from the platelets within seconds. Platelet factor 4 is strongly chemotactic for inflammatory cells and fibroblasts. It is at least 10 times more potent (on a mole to mole basis), however, than inflammatory cells in inducing fibroblast chemotaxis, and preferentially attracts fibroblasts into a wound.[8]

Platelet-activating factor is a large glycerophospholipid released from the cell membranes of platelets, neutrophils, eosinophils, macrophages, mast cells, and inflammatory cells. It is a potent inflammatory mediator, chemotactic for neutrophils and monocytes, and activates macrophages. Unlike growth factors, it is not mitogenic.[3]

Activation, phagocytosis, or lysis of the neutrophils releases contents of their granules into the extracellular space. These contents include enzymes such as elase and collagenase that can degrade the connective tissue at the wound site. Although this can assist in removal of damaged tissue, it also may cause further injury.[7]

Subsequent to accumulation of neutrophils in the wound, monocytes become evident in response to chemoattractants such as bacterial products, complement, and the most potent of all, TGF-β.[7] The monocytes remain at the injury site for days to weeks, during which time they participate in debridement, microbicidal events, and orchestration of the events of tissue repair. These processes are carried out through the release of molecules that act on other inflammatory and mesenchymal cells to regulate their function.[7]

Proliferation. Tissue repair begins as the inflammatory response subsides, although the process of inflammation is integral to initiation of fibroblast activity. Factors released from the platelets, monocytes, and macrophages, including PF4, PDGF, and TGF-β, contribute to fibroblast recruitment, proliferation, and matrix synthesis.[7] Monocyte-derived PDGF and TGF-β also promote angiogenesis, which is necessary for the formation of granulation tissue.[9] Further stimulation of matrix synthesis by these factors and others (interleukin-1 and tumor necrosis factor) leads to scar formation and injury repair.[7]

Maturation. The process of wound maturation involves a dynamic process of collagen degradation and reorganization to maximize the strength in the wound. Collagenase is the key enzyme in collagen degradation and is secreted by the fibroblast as procollagenase. Procollagenase is subsequently activated to collagenase, requiring a series of metallo-proenzymes requiring zinc.[10] However, cells that produce collagenase have also been shown to produce a collagenase inhibitor. These are collectively described as TIMP (Tissue Inhibitor of Metallo-Proteinases).[11] Growth factors can modulate collagenase expression by mesenchymal cells.[12] Both PDGF and TGF-β have been shown to induce procollagenase synthesis[13]; however, TGF-β can block procollagenase induction caused by other growth factors such as EGF.[14] In addition, TGF-β induces TIMP synthesis.[14] Thus, TGF-β is able to reduce new synthesis of collagen by cells and enhance the ability of cells to inhibit other sources of collagenolytic activity.

Biology of PDGF and TGF-beta

Platelet-derived Growth Factor

Platelet-derived growth factor is a large glycoprotein synthesized by platelet alpha granules and promotes initiation of the cell cycle and subsequent cell division.[15] The protein core of PDGF is a disulfide-linked dimer composed of two distinct but homologous polypeptide chains, A and B.[3,16,17] It is stable to heat, extreme pH, and many proteases. Platelet-derived growth factor exists *in vivo* in homodimer and heterodimer forms, all of which are biologically active.[17] The heterodimer form (PDGF-AB) is predominant in human platelets; however, PDGF-BB homodimer has been found in porcine platelets, and PDGF-AA has been found in numerous cell types, including tumor cells and activated fibroblasts.[16] Platelet-derived growth factor-like molecules are also synthesized by activated macrophages, endothelial cells, smooth and skeletal muscle cells, placental trophoblasts, mesangial cells, and astrocytes.[18]

Platelet-derived growth factor interacts with its target cells by noncovalent binding to a cell surface receptor that has a high affinity and selectivity for PDGF.[17] These receptors have been identified in fibroblasts, smooth muscle cells, glial cells, and chondrocytes.[17] The PDGF receptor consists of α- or β-subunits that are present in varying numbers on different cell types. The two chains of the PDGF dimers bind to the receptor molecule, resulting in dimerization of the receptor subunits. Receptor dimerization may be required for transmission of the mitogenic signal. The PDGF-α receptor binds both the A and B chains of PDGF and hence binds all isoforms of PDGF. The PDGF-β receptor, however, binds only the B chain of PDGF and hence binds only PDGF-BB and PDGF-AB.[17,19,20] The total number of receptors and the ratio of α and β receptors on cells may be important in determining the relative response to the different isoforms. This may play a role in autocrine regulation of the PDGF isoforms.[19,20]

Platelets are the largest source of PDGF but activated macrophages and fibroblasts also secrete PDGF.[20] Platelet-derived growth factor is chemotactic for monocytes, neutrophils, and fibroblasts.[20] Monocytes in the wound subsequently differentiate into wound macrophages. Platelet-derived growth factor is mitogenic for mesenchymal cells and stimulates collagen production by fibroblasts, probably through indirect mechanisms.[3] Activated wound macrophages and fibroblasts that secrete PDGF can be activated by PDGF, establishing a positive autocrine feedback loop within the wound that amplifies the initial platelet-derived signal and triggers release of growth factors and extracellular matrix proteins necessary for wound healing.[16,20] In addition, PDGF also stimulates collagenase, required for wound collagen remodeling.[13]

Transforming Growth Factor Beta

Transforming growth factor beta (TGF-β), also a disulfide-linked molecule,[6,21] is recognized by highly specific receptors that are present on almost every cell type.[6] Major sources of TGF-β during soft tissue repair are the platelet alpha granules and macrophages.[21] Transforming growth factor beta is present in wound fluid and is chemotactic for monocytes, macrophages, and fibroblasts, causes increased synthesis of extracellular matrix proteins including fibronectin, collagen, and glycosaminoglycans, decreases protease secretion and increases the secretion of protease inhibitors, and regulates macrophage cytokine production.[21] Using stainless steel wound chambers placed under the skin in rats, aspirates of accumulated fluid showed peak intrinsic levels of TGF-β during the most active fibroblastic, proliferative period (seven to 14 days).[22]

Effect on bone and cartilage. Transforming growth factor beta is important in the embryonic formation of cartilage and bone[23]; however, large amounts of TGF-β are found in adult bone. Transforming growth factor beta is a potent inducer of type II collagen and proteoglycans, components of the extracellular cartilage matrix.[21] Transforming growth factor beta is a mitogen for osteoblasts and stimulates their production of extracellular matrix. Increased levels of TGF-β have been found in the callus of healing fractures[21] and exogenous TGF-β has increased bone formation *in vivo* in rats.[24]

Suppressant activity. Transforming growth factor beta is a potent suppressant of lymphocyte proliferation and function, 10,000 to 100,000 times more potent (on a molar basis) than cyclosporine. It is produced by T and B cells and inhibits interleukins and other cytokines (tumor necrosis factor) that stimulate lymphocyte function.[21] Thus, an autocrine feedback loop exists, and TGF-β will inhibit proliferation of T cells stimulated by interleukin 1 or 2, inhibit proliferation and antibody production in B cells, depress cytolytic activity of natural killer cells, and inhibit the generation of cytotoxic T cells and lymphokine-activated killer cells.[21] Transforming growth factor beta may have potential as an immunosuppressive agent and has suppressed cardiac allograft rejection in mice.[21]

The role of TGF-β in carcinogenesis is not clearly understood. Transforming growth factor beta is a potent antiproliferative agent for most epithelial cells, however, cells normally suppressed by TGF-β may escape from autocrine control and become autonomous. This may be mediated through loss of TGF-β, loss of TGF-β receptors on the cell, or failure of the intracellular growth control pathway mediated by TGF-β.[25]

Development of agents that stimulate TGF-β secretion in premalignant epithelium, before it has lost sensitivity to TGF-β, may be useful in prevention of malignancy. Tamoxifen, often considered to be an antiestrogen agent, is a potent stimulator of TGF-β secretion.[26] Both tamoxifen and retinoids (retinoic acid and its analogs) have been successful in preventing breast and skin cancer in experimental animals.[21]

Inhibition of PDGF and TGF-β

The monocyte/wound macrophage is the major source of PDGF and TGF-β after platelet activation has occurred and is also responsible for the activation of TGF-β secreted by platelets and other cells. The targeted activation of the monocyte or wound macrophage may cause endogenous stimulation of fibroblast proliferation. Alternatively, negative modulation of fibroblast proliferation might be accomplished by inhibiting the release or activation, or both, of PDGF and TGF-β, or by stimulation of endogenous inhibitory substances such as beta fibroblast interferon (IFN-β).[17] This may contribute to pathologic fibrogenic processes such as keloid formation, exuberant granulation tissue formation, encapsulation of implants, abdominal adhesion formation, and entrapment of tendons after tendon repair.[17] Beta fibroblast interferon is produced and released by stimulated fibroblasts and functions as an autocrine inhibitor. Hemopoietic cells also produce beta-related interferons.[27] However, IFN-β shares a receptor with one other class of interferon (IFN-α), and all IFN families (IFN-α, -β, and -γ) are biologically active in a wide range of cell types, which may complicate their use.[17]

Role of PDGF and TGF-β in Wound Healing

The roles of PDGF and TGF-β in wound healing are best understood. Although wounds are never deficient in PDGF or TGF-β, the use of exogenous growth factors in normal and compromised tissue explains the action of these molecules and demonstrates potential for chemical manipulation of wound healing. Most studies use a refined

B homodimer PDGF derived from human platelets called recombinant PDGF-BB (rPDGF-BB) because it will act at both alpha and beta receptors on cells.

Platelet-derived growth factor acts initially as a chemotactic agent for monocytes, macrophages, and fibroblasts, then as a mitogen through the release of other factors from the macrophages. Recombinant PDGF-BB causes the influx of neutrophils in one to two days, then macrophages and fibroblasts by three to five days. The chemotactic activity of rPDGF-BB is sustained for 21 days.[6] Platelet-derived growth factor induces activated macrophages to secrete TGF-β both *in vitro* and *in vivo*.[6,20] Hence exogenous PDGF appears to act in part through the recruited macrophage and through endogenous TGF-β synthesis to activate the proliferation of fibroblasts and stimulate collagen production.[6,20] Macrophages and fibroblasts in incised wounds treated with PDGF contain significantly increased levels of intracellular TGF-β *in situ,* compared with untreated wounds.[28]

In comparison, TGF-β is a weaker chemotactic agent, but acts directly on the fibroblast, both as a chemotactic agent and then as a potent stimulator of collagen and fibronectin synthesis.[6] Only the influx of macrophages and fibroblasts within three to five days is observed and the chemotactic effect of TGF-β appears transient.[6] Importantly, the *in vivo* effects of TGF-β can occur independent of any significant recruitment of inflammatory cells into the wound.[6]

Neither PDGF or TGF-β alter the normal sequence of repair, but augment the rate and amount of extracellular matrix deposition, resulting in earlier wound closure.[2,15,29-31] Nor is the long-term outcome and wound strength of healthy wounds treated with PDGF and TGF-β different from untreated wounds.[15,29-31] Recombinant PDGF causes a dose-dependent increase in the volume of granulation tissue in a wound,[15] probably through the release of other growth factors or inflammatory mediators that have a direct effect on matrix remodeling. Incised wounds in hairless guinea pigs treated with rPDGF-BB had increased granulation tissue at seven days compared with untreated wounds.[15] All wounds were healed by 14 days, and the total time to reepithelialize was not different.[15]

A single application of rPDGF to full-thickness circular wounds in the ears of rabbits showed a 200% increase in volume of granulation tissue over untreated wounds at seven days.[2] By 182 days, however, the volume of granulation tissue in rPDGF-BB and untreated wounds were the same.[2] Recombinant PDGF-BB doubled the rate of re-epithelialization of the wounds and increased the amount of new vessel formation, an important component of granulation tissue. Recombinant PDGF-BB is not known to stimulate keratinocytes or endothelial cells directly, but may cause release of other growth factors from macrophages and fibroblasts.[2]

Transforming growth factor beta causes initial acceleration of granulation tissue formation but does not induce greater than normal amounts later in healing. This directly correlates with changes in the collagen content and wound strength.[29-31] In elliptical wounds in guinea pigs covered by heparin-impregnated collagen sponges with or without TGF-β,[29] wounds treated with TGF-β were significantly stronger and had a higher connective tissue content at 8 days, but were not different from untreated wounds at 14 days. In contrast to other studies,[32,33] re-epithelialization and wound contraction were not different between treated and untreated wounds.[29] Transforming growth factor beta accelerates the gain of wound strength by three days in the skin[6] and by four days in the gastrointestinal tract.[34] The gain is transient, however, with a peak gain in treated wounds by five to seven days, but not different from untreated wounds at 14 days.[34] Recombinant PDGF-BB does not give the same degree of accelerated gain of wound strength, taking at least seven days to increase over untreated wounds. The gain in wound strength with rPDGF-BB over untreated wounds persists at least 49 days, however, and remains accelerated during this time, by as much as five to 10 days.[5,28] By 89 days, the effect is gone.[28] The prolonged influence of rPDGF-BB correlates directly with the demonstration of enhanced TGF-β expression in both macrophages and fibroblasts in the wound.[28]

Despite increased wound collagen content and wound strength, several studies report suppressed epithelialization in wounds treated with TGF-β.[32,35,36] A study compared a single application of rPDGF-BB, TGF-β and insulin-like growth factor (IGF), alone or in combination on partial-thickness wounds in pigs. At seven days, wounds treated with TGF-β alone showed the most dramatic response. Transforming growth factor beta increased hydroxyproline content (a measure of collagen content) 213% over untreated wounds; however, it inhibited epithelialization and caused a 40% decrease over untreated wounds in epidermal thickness with dyskeratosis. Transforming growth factor beta combined with IGF did not alter the results from TGF-β alone. Recombinant PDGF-BB or IGF alone did not affect epidermal thickness at seven days, but did increase epidermal thickness over untreated wounds when used in combination.[36] This combined effect on the epidermis is likely to be indirect, through the release of other growth factors, because PDGF receptors on epidermal cells have not been identified.[36]

Use of Exogenous PDGF and TGF-β

The action of rPDGF-BB is substantiated by investigation of wound healing in irradiated rats. A single application of rPDGF-BB partially reversed impaired wound healing in rats receiving high-energy surface irradiation,

but had no effect on rats receiving total body irradiation.[37] Recombinant PDGF appeared to have a local wound effect, primarily on the monocyte/macrophage derived from bone marrow cells, rather than on mesenchymal-derived cells. The wound macrophage is derived from circulating monocytes and appears necessary to mediate rPDGF-BB activity. Total body irradiation destroys the bone marrow, demonstrated by a monocyte count in total body irradiated rats of only 7% that of nonirradiated wounds. This subsequently depletes the wound of these cells and hence limits any affect of PDGF.[37] This study also showed that rPDGF-BB does not directly influence dermal fibroblasts to synthesize collagen because many fibroblasts migrated into wounds in animals that had total body irradiation without an increase in wound strength.[37] Fibroblasts normally continue RNA and protein synthesis after irradiation with 800 rads; the rats in this study only received 200 rads and hence should have been capable of producing collagen.[36]

Application of rPDGF-BB on wounds in rats with glucocorticoid-induced impaired healing improved the rate of wound contraction. Rats given 10 mg cortisone IM for one to two days before surgery and five days a week after surgery, showed increased wound contraction with rPDGF-BB application. Normal rats showed 50% contraction by 6.5 days, rPDGF-BB treated impaired rats by 11.5 days, and untreated impaired rats by 13.5 days.[38]

The different effects of PDGF and TGF-β on wound healing is highlighted by a study on wounds in glucocorticoid-induced impaired wound healing in rats. Rats treated with methylprednisolone 30 mg/kg IM, two days before wounding showed a decrease in strength by 47% at 7 days (74% at 5 days) compared with wounds of healthy rats, and had a decrease in systemic white blood cell numbers to nearly undetectable levels within one day of wounding. Transforming growth factor beta applied at wounding increased wound strength at 7 days in impaired wounds by almost 200% over untreated impaired wounds. This increase was transient and TGF-β–treated impaired wounds were not different from untreated impaired wounds by 10 and 14 days. By this time, the effect of methylprednisolone was diminishing (indicated by a return in systemic white blood cell counts) and the effect of TGF-β was declining. In comparison, rPDGF-BB applied at wounding did not augment the wound strength of the impaired wounds at 7 or 10 days.[6] Neither TGF-β– nor rPDGF-BB–treated wounds showed any influx of monocytes or neutrophils, presumably a result of methylprednisolone administration. Because the monocyte/macrophage is responsible for initiating normal incision repair,[39] this study suggested that TGF-β is effective in improving wound strength through its direct influence on fibroblasts; PDGF, in contrast, requires the macrophage to mediate its activities on wound healing, probably through induced macrophage synthesis of TGF-β.[6] Hence, the methylprednisolone-induced absence of macrophages prevented any affect of PDGF. Transforming growth factor beta did not reverse the delay of fibroblast influx seen in wounds in rats given glucocorticoids. Procollagen type I was not detected until five days after wounding (normally it can be detected as early as two days), although at five and seven days, twice the number of fibroblasts were present in TGF-β– over rPDGF-BB–treated and untreated impaired wounds. The changes in fibroblast and collagen content correlated with the changes observed in wound breaking strength.[6]

Application of rPDGF to open wounds in genetically diabetic mice increased the volume of granulation tissue at 10 and 21 days and the rate of second intention wound closure over untreated diabetic mice.[40] Streptozotocin-induced diabetes in rats caused a decrease in the amount of collagen, DNA, and protein present in implanted sponges (a standard wound model). Transforming growth factor beta significantly increased the collagen content in implanted sponges in diabetic rats to levels found in untreated, normal rats. Application of TGF-β to incisions increased wound strength at 7, 14, and 21 days in untreated, normal rats, however, but not in diabetic rats.[40] These investigators suggested that the collagen of diabetics does not undergo normal maturation.[41] Although TGF-β increased the collagen content in diabetic wounds, it did not reverse the defect in collagen maturation and subsequently failed to improve wound strength.[41]

The exogenous use of growth factors offers promise for chemical manipulation of the healing wound. The clinical manipulation of wound disorders should exploit the fact that the healing process is the net result of the balance of both stimulatory and inhibitory signals within the wound site. Although addition of PDGF and TGF-β may be desirable to assist the healing in a compromised wound, inhibition of their release and effects by the addition of other factors such as fibroblast IFN-β may be desirable in wounds with pathologic fibrogenic processes.

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