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PROSPECTS

Role of Platelet-Derived Growth Factor in Wound Healing

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Abstract Platelet-derived growth factor (PDGF) is a potent activator for cells of mesenchymal origin. PDGF stimulates chemotaxis, proliferation, and new gene expression in monocytes-macrophages and fibroblasts in vitro, cell types considered essential for tissue repair. Therefore, we analyzed the influence of exogenously administered recombinant B chain homodimers of PDGF (PDGF-BB) on two experimental tissue repair paradigms, incisional and excisional wounds. In both types of wounds, as little as 20–200 picomoles applied a single time to wounds significantly augmented the time dependent influx of inflammatory cells and fibroblasts and accelerated provisional extracellular matrix deposition and subsequent collagen formation. In incisional wounds, PDGF-BB augmented wound breaking strength 50–70% over the first 3 weeks; in excisional wounds, PDGF-BB accelerated time to closure by 30%. PDGF-BB exaggerated, but did not alter, the normal course of soft tissue repair, resulting in a significant acceleration of healing. Long term observations established no apparent differences between PDGF-BB treated and non-treated wounds. Thus, the vulnerary effects of PDGF-BB were transient and fully reversible in both wound healing models. Furthermore, analysis of PDGF-treated and non-treated wounds has provided important insights into mechanisms of normal and deficient tissue repair processes. PDGF appears to transduce its signal through wound macrophages and may trigger the induction of positive autocrine feedback loops and synthesis of endogenous wound PDGF and other growth factors, thereby enhancing the cascade of tissue repair processes required for a fully-healed wound. Thus, PDGF and other wound produced polypeptide growth factors may be the critical regulators of extracellular matrix deposition within healing wounds.

Key words: tissue repair, macrophage, fibroblast, extracellular matrix, growth factors

Platelet derived growth factor (PDGF) is one of several polypeptide cytokines which control the growth, differentiation, and activation of a variety of diverse cell types [reviewed in 1]. Although initially characterized as a platelet derived mitogen specific for mesenchymally derived fibroblasts and smooth muscle cells [2–4], isoforms of PDGF are now known to be secreted from many activated cells, including macrophages, fibroblasts, and endothelial cells, and to participate in vulnerary activities as diverse as soft tissue repair, bone repair, and epithelial regeneration. Some of these activities may result from an interaction of PDGF with other growth factors in additive, synergistic, or antagonistic ways to regulate cellular activities. Other growth factors active in tissue repair include epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), and insulin-like growth factor (IGF) [5]. Each of these growth factors, including PDGF, belongs to a unique family of functionally related molecules. The growth factors identified appear to interact in complex and largely unidentified ways to affect essential normal physiologic processes as diverse as wound healing, morphogenesis and embryogenesis, and stem cell commitment [5]. The potential role of PDGF in physiologic functions and pathologic processes such as atherosclerosis and inflammatory diseases also has been the subject of recent interest [reviewed in 6].

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BIOLOGICAL ACTIVITIES OF PDGF IN VITRO

PDGF was first purified to homogeneity from human platelets and shown to be a highly cat-

ionic (pI 10) disulfide linked heterodimer of approximately 30,000 daltons consisting of A and B polypeptide chains which are ~60% homologous to one another (PDGF-AB) [1]. PDGF is stable to heat, extremes of pH, and many proteases, in part due to the stability conferred by 8 cysteine residues per chain in disulfide linkages; the dimeric form appears to be required for activity. The B-chain of PDGF is more than 90% homologous to the v-*sis* oncogene product of the simian sarcoma virus (SSV) [7,8], an acutely transforming retrovirus which was first isolated from fibrosarcomas in the woolly monkey. The normal cellular homolog, the product of the c-*sis* gene, the B chain of PDGF, was the first growth factor found to be related to a viral oncogene product [7,8]. Although the predominant product in human platelet α granules is a heterodimer [9], porcine platelets contain PDGF-BB, and PDGF-AA homodimers have been isolated from a number of cell types, including tumors (i.e., gliomas, osteosarcomas), tumor cell lines, and activated fibroblasts [1,6,10,11]. Some leukemic lines preferentially synthesize PDGF-BB. Activated macrophages, endothelial cells, placental trophoblast, smooth and skeletal muscle cells, mesangial cells, and astrocytes synthesize PDGF-like molecules which have not yet been definitively characterized [6,10,12–14]. In some cell types (i.e., endothelial cells), transcription of A chain and B chain mRNAs is discoordinately regulated [15].

PDGF is the principal mitogen in serum for mesenchymally-derived cells [2–4], and was the first growth factor shown to be chemotactic for cells which migrate into healing wounds, e.g., neutrophils, monocytes, fibroblasts, and smooth muscle cells [16–19]. PDGF induces chemotaxis as well as activation (i.e., granule release) in the physiologically relevant nanomolar range [20, 21].

The biologic activities of the 3 PDGF isoforms appear to be qualitatively similar to one another [22]. Each is capable of binding to one or both of two types of PDGF receptors, α and β, which vary in density on different cell types [23,24]. It appears that each of the 2 subunits of the PDGF dimer binds to a receptor molecule, with resulting dimerization of the receptors. This receptor dimerization may be required for transmission of the mitogenic signal. The PDGF A subunit preferentially binds α receptors, whereas the B subunit binds both α and β receptors. As a result, cells which possess solely β receptors will respond to PDGF-BB, but poorly or not at all to PDGF-AB or PDGF-AA. However, cells possessing only α receptors will respond to all 3 isoforms. On cells possessing both α and β receptors, the ratio of the 2, as well as the overall number of PDGF receptors, appears to determine the relative response to the different PDGF isoforms. Therefore, differential receptor expression on different cell types may provide another level of regulation of the activities of PDGF isoforms. Binding of PDGF to its receptor and dimerization leads to tyrosine autophosphorylation, intracellular signal transduction, induction of early response genes (i.e., c-*myc*, c-*fos*), autocrine stimulation (PDGF-A induction) and the range of cellular responses characteristic of PDGF [23,27].

PDGF AS A WOUND HEALING HORMONE

Classically, tissue repair has been divided into acute inflammatory, repair, and collagen remodeling stages [28–30]; more recent work comparing PDGF-stimulated wounds to their normal controls has suggested a more detailed description of these 3 phases of repair [22,31]:

1. Directed and sequential migration of neutrophils, macrophages, and fibroblasts into the wound over the first several days;
2. activation of wound macrophages and wound fibroblasts resulting in endogenous growth factor production, provisional extracellular matrix synthesis, fibroblast proliferation, and collagen synthesis during the next 2 to 3 weeks;
3. remodeling of the wound with active collagen turnover and cross-linking from 2 weeks to 1 year post-wounding.

Endogenous factor(s) which induce cellular migration into the wound and activate macrophages and fibroblasts have been postulated for over 60 years and are considered to be derived from the wound cells themselves such as platelets, macrophages, and fibroblasts [28]. The fibroblast is essential for adequate wound healing since it is the principal source of procollagen type I, the major collagen type required for wound strength [32]. The macrophage is also essential for wound healing since abrogation of macrophage influx into the wound results in significantly decreased fibroblast influx and collagen synthesis [33–35]. Thus, endogenous bioactive molecules released from macrophages are

likely essential components in the cascade of tissue repair [13,36].

PDGF may be considered as one molecule which may serve as a critical switch to initiate and direct the tissue repair process. Abundant indirect evidence implicates PDGF in normal wound healing. Platelets, the first cells to initiate tissue repair processes at the wound site, are the largest source of PDGF in the body [1]. Peripheral blood monocytes are chemotactically attracted to the wound where they differentiate into wound macrophages [13,33,35]. Activated wound macrophages have been shown to contain messenger RNA for both the B-chain and A-chain of PDGF and to synthesize and secrete PDGF-like molecules [6,12,13]. PDGF-, TGF-β, or interleukin-1-activated fibroblasts synthesize and secrete PDGF-AA homodimers [6,13, unpublished observations]. Endothelial cells constitute a significant proliferating and differentiating population within early healing wounds. Although they do not appear to be responsive to PDGF, endothelial cells contain messenger RNA for PDGF-A and PDGF-B chains and secrete PDGF-like molecules [1,15]. Thus, the principal cell types entering wounds within the first several days are all capable of synthesizing and secreting PDGF into the wound milieu. Since PDGF secreting macrophages and fibroblasts also can be activated by PDGF, a positive autocrine feedback loop is likely operating within the wound to amplify the initial platelet derived signals and trigger a cascade of molecules (i.e., growth factors and extracellular matrix proteins) leading to a fully healed wound [5,36]. In vitro, PDGF stimulates synthesis of fibronectin and hyaluronic acid [37,38], two critical constituents of provisional extracellular matrix within wounds [39]. In addition, PDGF stimulates collagenase, required for wound collagen remodeling [40].

PDGF thus has the potential to direct or positively influence the major activities required for a normal wound healing response. However, since PDGF deficiency states have not been identified naturally or experimentally, endogenous wound PDGF has not been conclusively demonstrated to play a critical role in tissue repair, nor to act independently of other polypeptide cytokines. The redundant biological activities of growth factors (i.e., PDGF, FGF, IGF, EGF, and TGF-β) have made formal proof of PDGF's role in wound healing difficult to achieve experimentally. Nonetheless, the continued identification of specific and unique activities mediated by growth factors and their specific receptor interactions on target cells will increasingly permit the experimental dissection of each stage of wound healing.

THERAPEUTIC POTENTIAL OF PDGF

A second approach to understanding the role(s) of PDGF in the wound healing process is to apply PDGF directly to experimentally designed wounds. Grotendorst, Sprugel, and their coworkers first identified an augmentation of tissue repair processes mediated by PDGF contained within dead space chambers implanted into rats [41,42]. Although dead space chambers are not "true" wounds and have altered kinetics of tissue ingrowth compared to wounds, these initial experiments permitted the detection of vulnerary activities mediated by polypeptide growth factors which might be important in accelerating the healing of wounds [reviewed in 5].

Although experiments using dead space chambers suggested an important role for PDGF in augmenting tissue repair [41,42], we chose to examine its activities in experimental wounds in order to better identify and delineate mechanisms of PDGF-augmented repair. Recombinant human PDGF-BB homodimeric protein was produced in Chinese hamster ovary (CHO) cells which had been transfected with a PDGF-B gene driven by the SV40 early promoter [Thomason et al., manuscript in preparation]. A stable transfectant was selected and active PDGF-BB was purified to homogeneity from the conditioned medium. We have tested the local application of exogenous recombinant PDGF-BB in two recently described experimental wound models, incisional wounds in rats and excisional wounds in rabbits, and observed dose-dependent acceleration of tissue repair processes [22,43]. Within 3 weeks following a single application of PDGF-BB (200 pm) to incisional wounds in rats, wound breaking strength increased to 150–170% of normal control wounds [22]. The increased strength produced an acceleration of healing by 4–6 days over the first 2 weeks and by 5–10 days between 2 and 7 weeks post-wounding [31]. By 89 days post-wounding, both PDGF-BB-treated and control wounds had achieved similar wound strength (approximately 90% of unwounded dermis), indicating that the effect of a single application of PDGF-BB, although long lasting, is transient.

Cellularity and granulation tissue formation were significantly increased after a single appli-

cation of PDGF-BB to treated incisional wounds relative to control wounds during the first 21 days post-surgery (Fig. 1). Wounds treated with PDGF-BB demonstrated a highly exaggerated inflammatory response, characterized within 12 hours by increased neutrophil influx, markedly increased macrophage influx from days 1 to 4, and significantly increased fibroblast influx from 2 days persisting through 21 days post-wounding (Fig. 1) [22]. Increased numbers of procollagen containing fibroblasts were detected as early as 2 days post-wounding and also were increased through 21 days [44]. In contrast, procollagen containing fibroblasts do not begin migrating into normal incisional wounds until day 3. From days 28–89, fibroblast and granulation tissue content in PDGF-BB-treated and control wounds were similar, indicating the normal resolution of the PDGF-induced acceleration of the wound healing response [31]. Thus, PDGF-BB significantly accelerated normal tissue repair processes through transient recruitment and activation of macrophages and fibroblasts in this in vivo model, events entirely predicted based upon its in vitro effects on these two cell types (Fig. 1).

A quantitative model of excisional tissue repair has not been available previously in animals due to the positive influence of the superficial dermal muscle layer, the panniculus carnosus, on wound contraction. Since wound contraction is of lesser importance and a less desirable outcome of healing in man, a wound healing model was developed which would permit quantitation of new granulation tissue ingrowth in the absence of contraction. Circular excisional wounds 6 mm in diameter were placed through the dermis of the rabbit ear to the level of underlying cartilage [43]. The cartilage prevented the wound margins from contracting and permitted ingrowth of extracellular matrix from the wound margins. The new matrix was quantitated by histomorphometric techniques using a calibrated lens micrometer [43,45].

A single application of PDGF-BB (as little as 20 pm) increased the calculated volume of granulation tissue to 200% of control wounds after 7

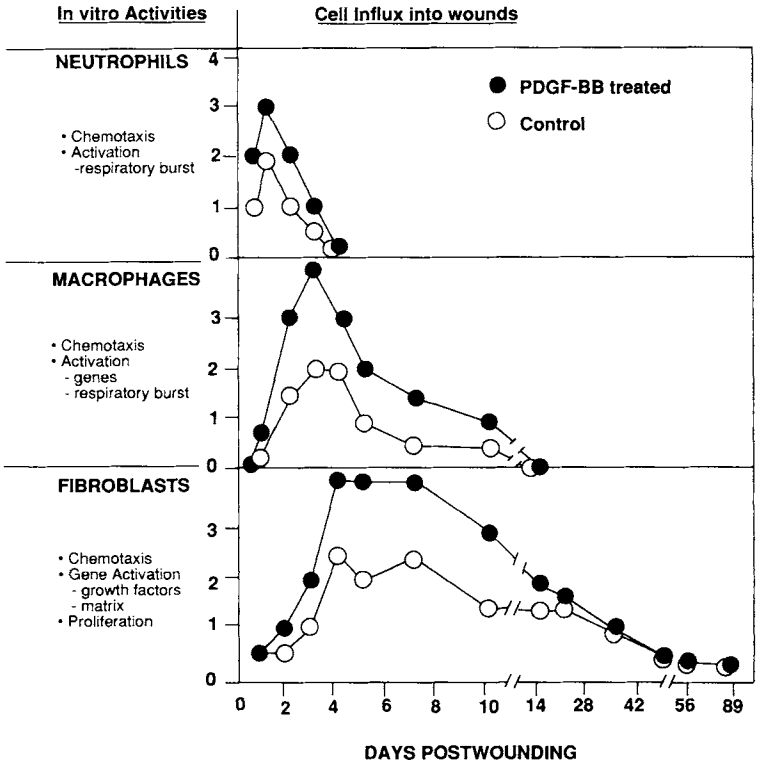

Fig. 1. Time-dependent cellular influx into PDGF-BB-treated and paired control incisional wounds in rat dermis. Cellularity was assessed on an arbitrary 0–4 scale by two independent, blinded observers from 12 hours to 89 days post-wounding. Neutrophil influx into wounds peaked at 1 day, monocyte-macrophage influx peaked at 2–4 days, and fibroblast accumulation was maximal between 4–7 days postwounding. PDGF-BB reversibly augmented and accelerated cellular influx into wounds [22,31].

days [43]. The granulation tissue induced by PDGF-BB consisted of predominantly fibroblasts (Fig. 2). Large amounts of extracellular matrix were observed at the leading edge of the wound, and a marked increase in the depth of new tissue 7 days after wounding was reprod ibly observed [43, Table I, Fig. 2].

Surprisingly, two features of PDGF-BB-hanced healing were noted which were not p dicted by the known in vitro activities of PD(

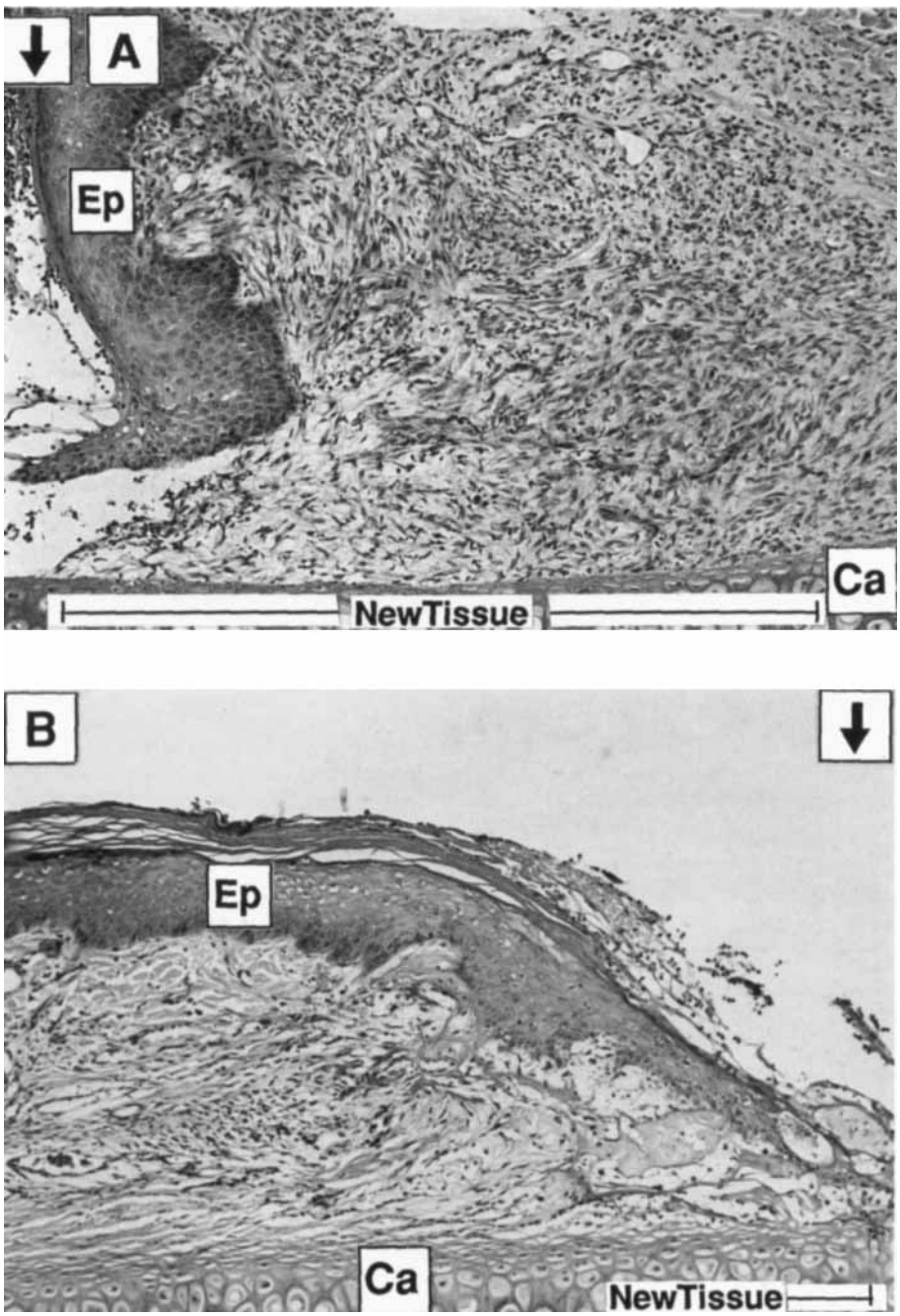

Fig. 2. Granulation tissue content in dermal excisional wounds placed on the rabbit ear. PDGF-BB-treated (**A**) and control (**B**) wounds were bisected after 7 days, and new tissue deposition was quantitated using a lens micrometer [43]. The leading edge of new tissue deposition is shown in representative PDGF-BB-treated and untreated wounds. Note the surface of the PDGF-BB-treated wound is not visualized in this cross section, due to enhanced granulation tissue formation. Both matrix deposition and fibroblast accumulation were markedly increased in PDGF-BB-treated wounds, as assessed by matrix-specific stains [43,45]. Arrows, leading edge of new matrix deposition within the wound; Ep, epithelium, Ca, cartilage; 100× original magnification, hematoxylin and eosin stain.

TABLE I. Transient Stimulation of Dermal Ulcer Healing With PDGF-BB*

Day post-wounding	Maximum depth of new granulation tissue (mm)[a]		
	PDGF-BB	Control	*P* value[b]
7	1.02 ± .06	0.76 ± .03	0.001
28	1.31 ± .31	1.12 ± .27	NS
64	0.58 ± .12	0.43 ± .17	NS
182	0.32 ± .08	0.33 ± .04	NS

*5 μg PDGF-BB was applied to wounds a single time on the day of surgery, and wounds were harvested at the indicated times.

[a]Unwounded dermis is 0.30–0.40 mm in diameter from the cartilage to the epidermis. The measurement is made at the point of greatest depth at the leading edge of the wound. Mean ± SEM, n = 4–7 samples.

[b]Unpaired student's t-test. NS, not significant.

First, PDGF-BB treatment doubled the rate of complete re-epithelialization of these wounds, although it is not known to have a direct effect on keratinocytes [43]. The increased keratinocyte migration and proliferation presumably results from recruitment of activated macrophages and fibroblasts by PDGF-BB, which in turn may secrete specific epithelial cell growth factors, such as transforming growth factor-α (TGF-α) or keratinocyte growth factor (KGF). Alternatively, activated wound keratinocytes may respond directly to PDGF-BB. Second, increased neovessel formation also was observed and was an important component of the increased granulation tissue present in PDGF-BB-treated wounds, although PDGF-BB is not known to stimulate endothelial cell proliferation and differentiation directly. Perhaps similar to its inductive effects on epithelial cells, PDGF-BB presumably induces specific endothelial cell mitogen(s) and differentiation agent(s), such as the fibroblast growth factors or platelet-derived endothelial cell growth factor, to stimulate angiogenesis. Importantly, the significant increase in granulation tissue formation mediated by PDGF-BB was fully reversible (Table I), as was observed in the incisional model.

The accelerated provisional matrix deposition induced by PDGF-BB consisted largely of glycosaminoglycans, including hyaluronic acid [45]. Later in the healing process, collagen fibrils and mature collagen bundles accumulated, indicating progression to a normally maturing wound as assessed by specific histochemical stains [45]. Thus, similar to observations made with the incisional model, PDGF-BB did not alter the normal sequence of repair, but augmented the rate and amount of provisional matrix deposition, resulting in a more rapid wound closure.

In analyzing tissue repair processes influenced by PDGF, we observed that PDGF appeared to require the wound macrophage for in vivo function. Animals pretreated with glucocorticoids or total body irradiation had a sharply reduced influx of wound macrophages and subsequent PDGF-accelerated incisional repair was abrogated [34,35]. In the pretreated animals, PDGF was able to attract increased fibroblasts into the compromised wounds, suggesting that the wound fibroblast appeared to require wound macrophage function, perhaps for activation to synthesize the new collagen required for increased wound strength. In vitro, PDGF is capable of activating growth factor and fibronectin gene expression in fibroblasts. PDGF does not appear to stimulate fibroblast procollagen type I synthesis directly [37,46]. However, PDGF-activated macrophages and fibroblasts synthesize TGF-β1 [31], which is a potent activator of the fibroblast procollagen type I gene [46,47]. Therefore, TGF-β1 may represent the final common signal for accelerated collagen formation in PDGF-treated wounds. In support of this hypothesis, macrophages and fibroblasts in PDGF-treated incisional wounds were recently shown to contain significantly increased levels of intracellular TGF-β protein in situ, compared to control wounds [31].

The treatment of wounds with exogenous PDGF-BB in supraphysiologic concentrations initiates and sustains a positive influence on wound healing. Its mechanism may involve the induction of an autocrine feedback loop, leading to an endogenous cascade of new cytokine synthesis within the healing wound during the acute inflammatory phase of repair (Fig. 3). PDGF-BB-stimulated fibroblasts appear to be activated by this cascade to produce quantitatively increased levels of procollagen type I, possibly mediated by new synthesis of TGF-β1 within wounds [44], in addition to increased levels of other matrix constituents during the repair (matrix deposition) phase.

Importantly, other investigators, utilizing other excisional wound models, also have demonstrated the vulnerary potential of PDGF to enhance normal and reverse deficient dermal repair [48–50]. Lynch and coworkers demonstrated accelerated healing of porcine partial thickness excisional wounds utilizing PDGF in combina-

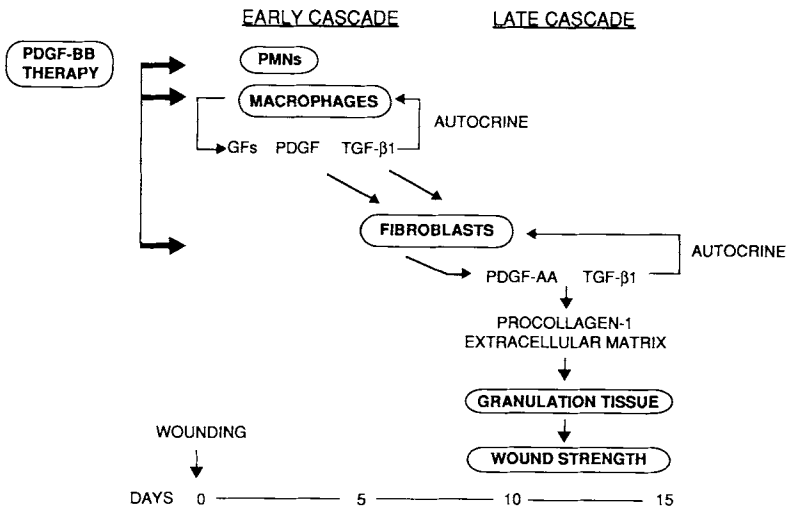

Fig. 3. Mechanism of action of PDGF-BB in dermal wounds. PDGF-BB augments the acute inflammatory phase, resulting in an enhanced cascade of activities inducing matrix deposition in the repair phase of wound healing. GFs, growth factors; PMNs, polymorphonuclear leukocytes.

tion with other growth factors, such as insulin-like growth factor I [48,49]. However, the doses utilized in these studies were considerably less than those found to be effective in the models described above, perhaps accounting for the lack of effect observed in porcine wounds treated with PDGF alone. PDGF-BB was also shown to accelerate healing of full thickness excisional wounds in the db/db mouse, at doses comparable to those utilized in our excisional wound model [50]. Thus, in both surface irradiation and diabetic-impaired wound healing, local administration of pharmacologic doses of PDGF-BB reverses deficient repair [35,41,50].

Continued investigations of PDGF mediated biological activities have revealed roles for this growth factor in other systems potentially important for wound healing, including antiinflammatory activity [51], uterine smooth muscle hypertrophy [52], lens growth and transparency [53], and central nervous system gliogenesis [54]. These diverse observations should permit rational testing of PDGF's repair potential in relevant non-dermal tissues.

CONCLUSIONS

PDGF, originally identified as the most potent mitogen in serum for cells of mesenchymal origin, now appears to be a critical regulator of the healing process. Soft tissue repair paradigms have revealed that PDGF treatment accelerates and augments normal repair [22,31,41–43,45] and can reverse deficient repair states in animals [35,41,50]. The utilization of PDGF in the healing wound coupled with continued analysis of its in vitro properties will further provide the scientific basis for understanding the normal wound healing process and suggest the potential for the use of PDGF as a therapeutic agent. The studies described above suggest PDGF-BB transiently exaggerates the acute inflammatory phase of repair [31,45], thereby accelerating the normal cascade of tissue repair processes, leading to earlier matrix deposition (Fig. 3).

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